NICE National Institute for Health and Care Excellence

Patiromer for treating hyperkalaemia

Chair's presentation

2nd appraisal committee meeting

Committee B, 29 October 2019

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Chair: Amanda Adler

ERG: Warwick Evidence

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Company: Vifor Pharma

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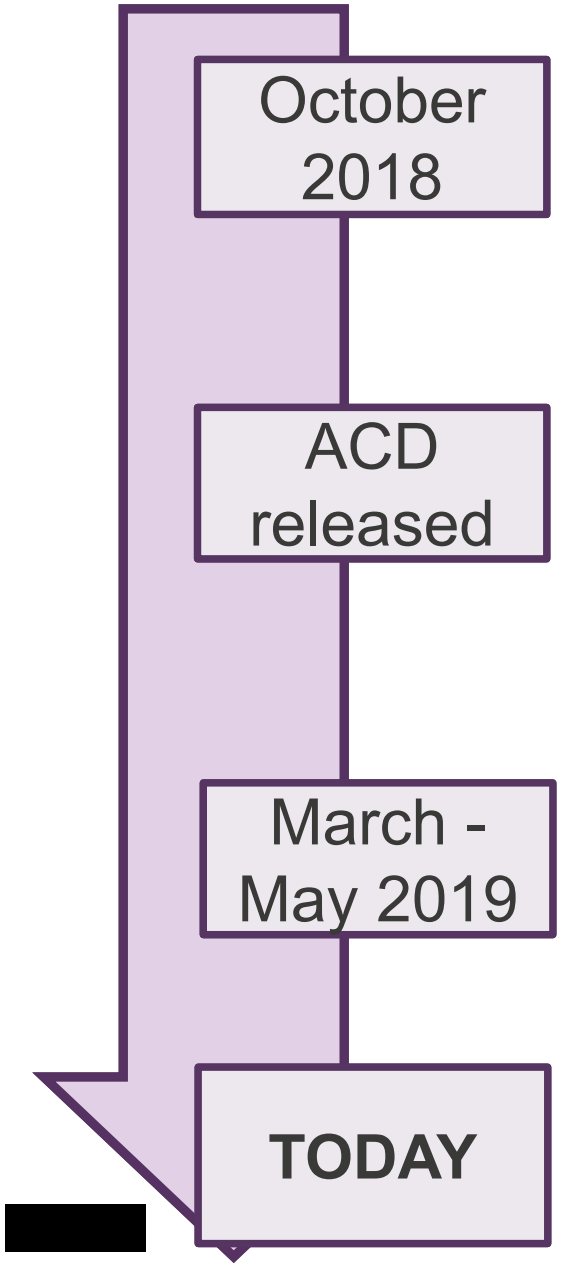
History of appraisal

ACD = appraisal consultation document, PAS = patient access scheme



- Patiromer considered at same time as sodium zirconium cyclosilicate (same indication)
- Not recommended

Company requested delay to:

- enable some trials to complete/mature
- collect additional evidence from clinicians
- significantly restructure model

Sodium zirconium cyclosilicate considered 2x further by committee: positive guidance released

Consider company and other stakeholder responses to ACD: new evidence, new modelling, increased PAS discount

Appraisal Consultation Document (ACD): preliminary recommendation

- Patiromer is not recommended:
  - no evidence to show patiromer extends life or improves quality of life compared with standard care
  - clinical trial results not relevant to NHS clinical practice; most people in trial had lower serum potassium (K^+) levels than would be treated in the NHS
  - cost effectiveness estimates are not valid, because of lack of relevant clinical evidence

[redacted]

How QALYs accrue

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

People on patiromer stay on renin-angiotensin-aldosterone system inhibitors (RAASi) longer so less likely to die of end stage renal disease (ESRD) or cardiovascular events *(Xie et al. 2016)*

Patiromer: More time spent in chronic kidney disease 3 and 4 states with better quality of life than ESRD state. Driven by staying on RAASi for longer. *(Landray et al. 2010)*

Patiromer: fewer episodes of hyperkalaemia related events such as hypomagnesemia, diarrhoea, constipation and nausea *(3 sources; same as TA 599 sodium zirconium)*

Length of life

Quality of life

Increased quality-adjusted life years

[redacted]

Key Issues

- Company has modelled population in line with committee's preferences in sodium zirconium cyclosilicate appraisal. Treat patients at or above serum potassium 6.0 mmol/L
  - is this reasonable?
  - if so, is the clinical data robust enough to populate the model?
- Regarding how long people continue to take patiromer, company chooses not to use trial data but instead use US observational data. Which is more appropriate?
- Is patiromer innovative?
- Any equality issues?

[redacted]

Current management of hyperkalaemia

Committee discussion:
Treatment starts when serum K^+ is **>6.0mmol/L**
- in line with NICE clinical guideline for chronic kidney disease in (CG182; ACD 3.1)

European Resuscitation Council definition	Current NHS practice	Company positioning
Mild hyperkalaemia 5.5 to 5.9 mmol/L	• Low K^+ diet • Adjust medicines that increase risk of hyperkalaemia (e.g. RAAS inhibitors)	**Patiromer**
Moderate hyperkalaemia 6.0 to 6.4 mmol/L		
Severe life-threatening hyperkalaemia ≥6.5 mmol/L	• Above plus: • Active treatments to reduce serum K^+ (e.g. IV insulin, IV glucose, calcium resonium)	

Abbreviations: K^+, potassium; IV, intravenous

TA599 September 2019: Sodium zirconium cyclosilicate recommended

Not a multiple technology appraisal

- Emergency care for acute *life threatening* hyperkalaemia alongside standard care
- Outpatient care for people with *persistent* hyperkalaemia and chronic kidney disease stage 3b to 5 or heart failure, if:
  - serum potassium level is ≥6.0 mmol/litre
  - not taking optimised dosage of RAAS inhibitor, and
  - not on dialysis
  - Stop sodium zirconium cyclosilicate if RAAS inhibitors are no longer suitable

[redacted]

Patiromer (Veltassa®)

Marketing authorisation	"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** • Take with food; separate 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 **= simple discount patient access scheme**

RAAS inhibitors, serum K^+ and outcomes –

Company's conceptual role for patiromer

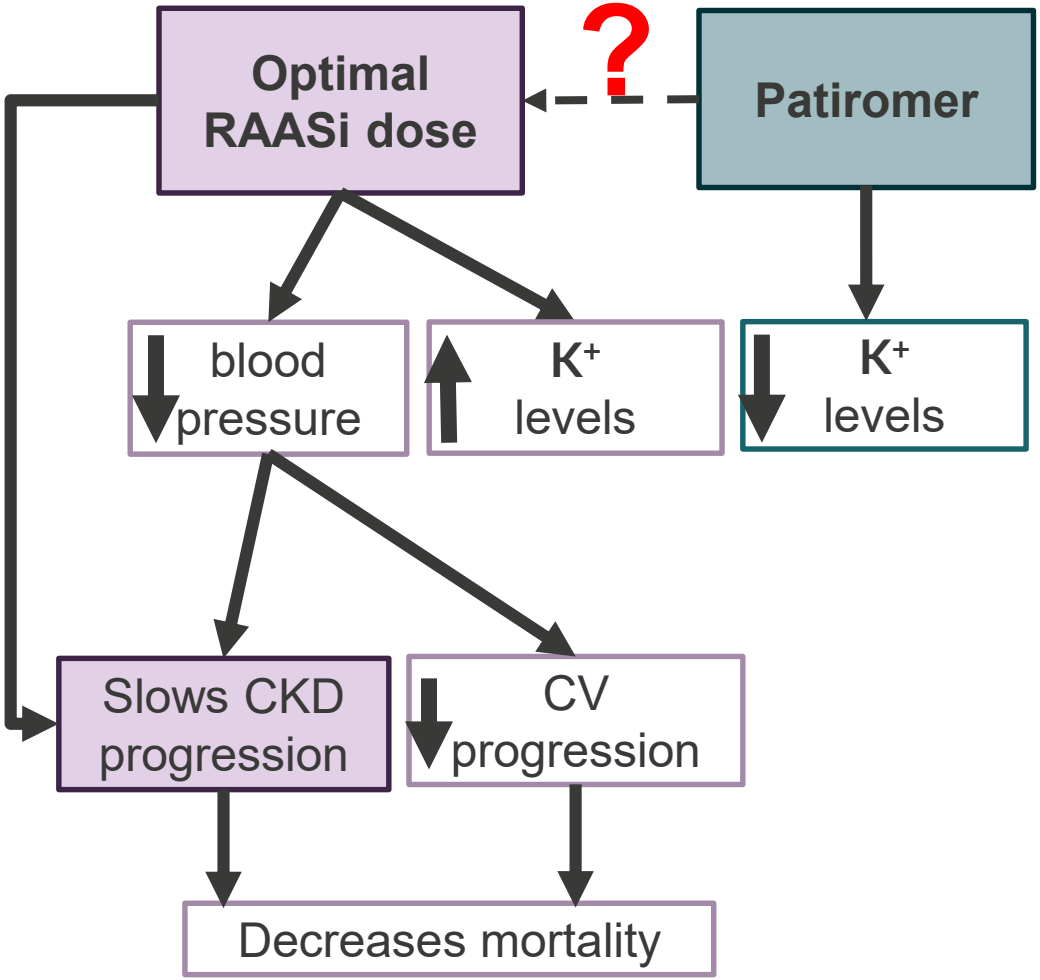
Committee discussion:

- Long-term benefit of continuing RAAS inhibitors varies (ACD 3.4)
- No evidence that patiromer prolongs survival (ACD 3.12)

RAASi: (e.g. ACE inhibitors, ARBs etc.)

- used to treat hypertension, heart failure, CKD
- reduce progression of renal disease, heart failure and cardiovascular mortality

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



Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin-receptor blockers; CKD, chronic kidney disease; K^+, potassium

Clinical evidence: OPAL-HK

Randomised controlled period includes people who responded to patiromer

Committee discussion:
Results of OPAL-HK not generalisable to the NHS (ACD 3.9, 3.10)

- Treatment in OPAL-HK started at lower serum K^+ (>5.1mmol/L) than would be treated in NHS (>6.0 mmol/L)

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, **n=92**

4.2 g patiromer 2x/day

K^+ 5.5 to <6.5 mmol/L. **n=151**

8.4 g patiromer 2x/day

n=15

n=92

PART B: Randomised 'single blind*' withdrawal phase **8 weeks**

n=107
Inclusion criteria

- People who **responded** to patiromer in part A
- People still having patiromer and RAASi

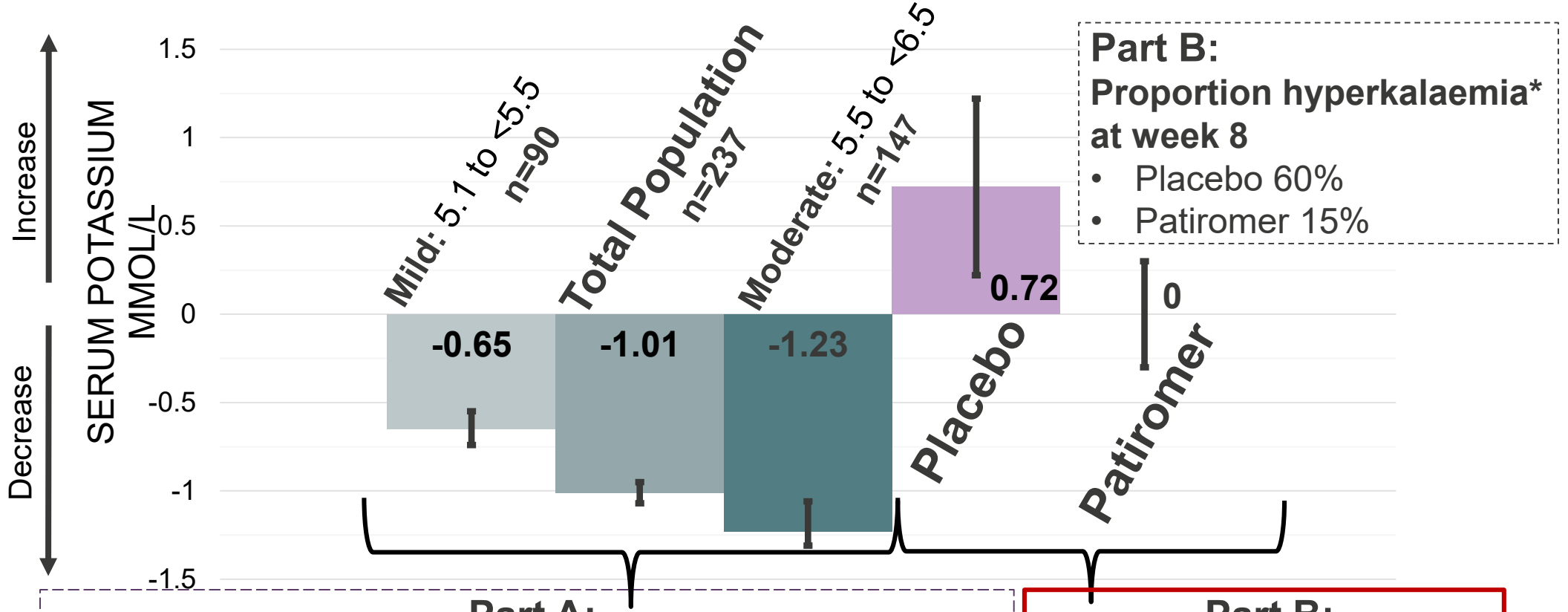
Patiromer n=55

Placebo n=52

ERG: trial not designed to examine all-cause mortality or cardiovascular events

Single-blind: *Patients blinded to treatment assignment but aware that all participants receive patiromer at some point. Investigators unblinded, to allow for appropriate management.*

Results OPAL-HK: change in serum potassium



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

Committee discussion:
- Results of OPAL-HK not clinically meaningful (ACD 3.7)
- At study end, potassium levels in both arms lower than would be treated in NHS

[redacted]

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

Relationship between RAASi and mortality

Committee discussion:

- Considerable uncertainty about using evidence for people starting RAAS inhibitors to model people stopping them (Xie et al)

- Xie et al. is a systematic review and network meta-analysis comparing starting RAASi (ACE and ARBs) with placebo or active controls
  - 119 trials, ~65,000 patients, patients with chronic kidney disease (any stage)
  - Company uses this paper to support life-extending benefit of RAASi

Company: literature review findings identify Xie et al. network meta-analyses as best source of long-term efficacy data to use in economic model

TA599 sodium zirconium cyclosilicate for treating hyperkalaemia (FAD 3.12): starting RAAS inhibitors prolongs life for many people, so stopping them for people who benefit from them would likely shorten life

[redacted]

Committee's considerations/ company response

Issue and ACD section	Committee's conclusion	Company's response
Serum potassium levels above normal range not always treated (3.1)	• Committee and clinical experts agreed they would not usually treat ... serum potassium levels <6.0 mmol/L	• Survey of clinicians • Updated base case serum potassium levels ≥ 6.0 mmol/L
OPAL-HK not clinically meaningful (3.7)	• At trial's end ... K+ lower than would be treated	• New data from AMBER trial
Results of OPAL-HK not generalisable to NHS (3.9, 3.10)	• People in the NHS more likely to be women, younger and have fewer comorbidities than in OPAL-HK	• Survey of current management of RAAS inhibitor-induced hyperkalaemia • New data AMBER trial
No evidence that patiromer prolongs survival (3.12)	• OPAL-HK did not collect data on progression of CKD, CV events or mortality • Observational study subject to bias	• Literature search • **ERG:** company does not provide evidence to support that patiromer extends life

Committee's considerations/ company response

Issue and ACD section	Committee's conclusion	Company's response
Risk of progressing to end-stage renal disease (3.14, 3.15)	• Considerable uncertainty about using evidence for people starting RAAS inhibitors to model people stopping them • Company likely overestimates uncertain benefit of continuing RAASi	• Literature search to support Xie et al for stopping RAASi • CKD 3 and 4 now as separate health states (previously one health state)

Proportion of episodes of hyperkalaemia resulting in hospitalisation (ACD 3.17)	• Proportion of episodes of hyperkalaemia resulting in hospitalisation was overestimated by company (100%) and ERG (24.3%)	• Company updated monthly proportion of hospitalisations because of hyperkalaemia
		• For patients with K+:
		  • > 5.0, 4.54%
		  • 5.5 to 6.0 mmol/L, 6.07%
		  • >6.0 mmol/L, 9.05%

Adverse events in model (ACD 3.18)	• Company should include adverse events in model	• Updated model includes adverse events

ACD consultation responses

Comments from:

- Vifor Pharma - patiromer
- Pumping Marvellous Foundation
- Royal College of Pathologists (no comments)
- Renal Association
- British Society for Heart Failure

Company new evidence	Used by company in model?
Review of clinical evidence	No
Survey of clinicians on how to manage RAASi with high K^+	No
Survey of heart failure patients	No
New trial evidence from PEARL-HF, AMBER	No
Clinical practice research datalink (CPRD) analysis	Yes, to model CKD 3 to CKD 4 transitions and standard of care changes in K+
US claims data for patiromer	Yes, to model stopping patiromer
Changed economic model structure	Yes
Increased discount	Yes

Patient and professional comments on ACD

- Patiromer could help facilitate safer use of renin angiotensin blockers or angiotensin receptor blockers in CKD and/or cardiac failure to maintain triple therapy
- Patiromer could provide options to prevent recurrent hyperkalaemia
- ‘British Society for Heart failure feel strongly that in routine clinical practice many clinicians ‘treat’ at potassium values much lower than 6.0 mmol/L.’ by reducing or stopping treatment with RAASi
- Alternatives are needed to calcium resonium, which frequently causes gastrointestinal side effects

[redacted]

Company's new evidence: clinical practice

Aligns with clinical expert views from 1st committee meeting

1. **Published survey:**
   - Survey sponsored by: Vifor Pharma
   - n=112 healthcare practitioners of cardiorenal patients
   - 81% from UK and Europe, 19% countries not stated
   - 65% doctors: 38% consultants, 23% training grades, 5% GPs
     - **Results: 'action' at K+ of 5.7 or 5.8 mmol/L**
   - ERG: only doctors would treat hyperkalaemia in UK
2. **Company survey:** modified Delphi method, interviews and web based or face to face discussions of consultant level cardiologists and nephrologists
   - Telephone interview 1st round n=10, 2nd round n=21, working group n=9
   - Maximum tolerable serum potassium level 5.5 to 5.9 mmol/L for all cardiologists and most nephrologists
   - Consensus to down-titrate or stop RAASi at K+ >6.0mmol/L

[redacted]

Company's new clinical evidence: PEARL-HF

company did not use in model; ERG not relevant to scope

PEARL-HF randomised double blind

- **Aim**: determine efficacy and safety of patiromer
- **Population**: 105 people with a history of hyperkalaemia resulting in stopping RAASi and/or beta-andrenergic blocking agent AND
  - heart failure, OR
  - CKD with an eGFR <60 mL/min/1.73m^2
- **Intervention**: patiromer + spironolactone
- **Comparator**: placebo + spironolactone
- **1º outcome**: change from baseline in serum K+ to end of 28 day treatment period

Company: the placebo group in **PEARL-HF** is generalisable to the current standard of care in people with heart failure treated with RAASi

ERG: Participants did not have hyperkalaemia at baseline, not relevant to scope.

Question to company – which of committee's conclusions does this address?

[redacted]

Company's new clinical evidence: AMBER

company did not use in model; ERG not relevant to scope

AMBER randomised double blind

- **Aim**: determine if patiromer results in more persistent use of spironolactone
- **Population**: 295 adults with serum potassium 4.3 to 5.1 mmol/L, CKD eGFR 25 to ≤ 45 mL/min/1.73m^2 , uncontrolled high blood pressure, taking at least 3 medications for blood pressure
- **Intervention**: patiromer + spironolactone
- **Comparator**: placebo + spironolactone
- **1º outcome**: treatment group difference in % on spironolactone at week 12

Company:

- **AMBER** demonstrates that patiromer enabled a significantly higher proportion of patients to continue spironolactone (20% more)

- **ERG: AMBER** did not provide any more evidence on the clinical effectiveness of patiromer compared with standard care

[redacted]

Company's new clinical evidence: DIAMOND

ongoing trial

- Ongoing, estimated completion March 2022
  - Sites in USA*
  - Patiromer vs placebo
  - **Population**: n=2,388
    - Adults with hyperkalaemia (K+ >5.0mmol/L) and heart failure receiving beta blocker with hospitalisation for heart failure or treatment in outpatient setting within last 12 months OR
    - Normal K+ (4.0 to 5.0 mmol/L) but previously high in last 12 months causing discontinuation of heart failure medication
  - **1º outcome:** time to first occurrence of cardiovascular death or hospitalisation

Question for company: Is this a superiority or non-inferiority study?

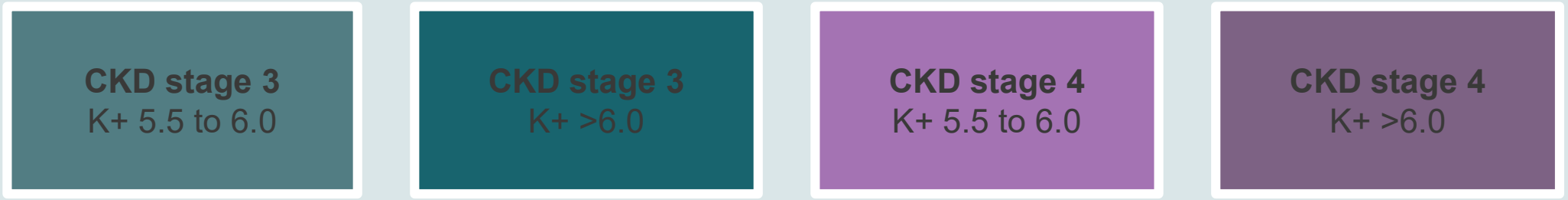
[redacted] * Factual inaccuracy identified during meeting by company, DIAMOND also has sites in UK

Company's updated model

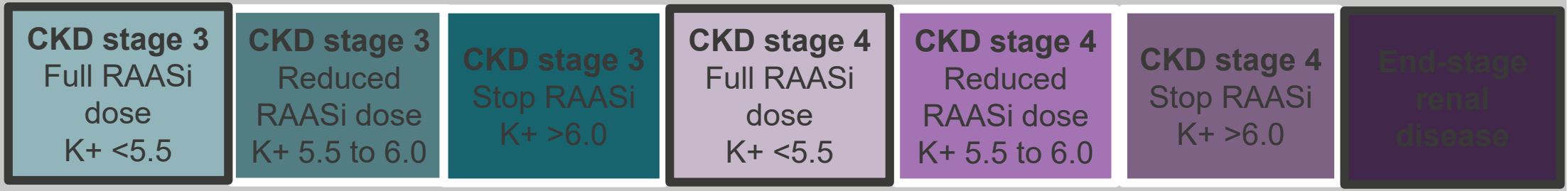
Major revisions to model structure in response to consultation

Starting health states

- Patients start grouped by:
  - CKD 3 or 4, and
  - K+ levels 5.5 to 6.0 mmol/L or >6.0 mmol/L
- Proportion in each state based on part A of OPAL-HK
- In cycle 1, patiromer associated with increased costs and loss of utility from adverse events
- Benefit of patiromer only arise after 1st cycle when K+ reduces



- **Health states after first cycle (1 month)**
- After first cycle: potassium levels can reduce <5.5 mmol/L
- After second cycle: CKD stage 4 can progress to ESRD, and can have cardiovascular event



Company's revised population

aligned with committee's preferences in ACD

- Data in model for patiromer from OPAL-HK
- Data for comparator arm from company analysis of people with CKD stage 3/4 with RAASi therapy prescriptions from the UK Clinical Practice Research Datalink (CPRD)
- Company use non-trial data because no control arm in OPAL-HK part A

Previous population	Revised population
serum potassium 5.1 to 5.5 mmol/L	serum potassium ≥6.0 mmol/L

ERG comments:

- **Company population based on a small numbers:**
  - **n=** [redacted] for patiromer from OPAL-HK trial
  - **n=** [redacted] from CPRD
- Unclear how missing data has been handled

[redacted]

OPAL-HK and CPRD

ERG: data sources may not be comparable

- ERG: Baseline characteristics are very different
  - also implies OPAL-HK patients not representative of UK population

	CPRD	OPAL-HK
Female (%)	[redacted]	42
Average age (year)	[redacted]	65.0
eGFR (ml/min/1.73 m^2)	[redacted]	39.0
Proportion with diabetes (%)	[redacted]	63
Proportion with hypertension (%)	[redacted]	96
Proportion with heart failure (%)	[redacted]	42
Previous myocardial infarction (%)	[redacted]	27

- There might be placebo and other trial effects in OPAL-HK not present in CPRD
- Patients recruited to OPAL-HK were on RAASi at baseline, but in the CPRD it appears patients are starting RAASi at baseline

What is the most appropriate source of data for usual care?
Is adjusting for differences important?

ERG comments on model structure

- Model does not allow transitions observed in CPRD data; can only move 1 health state at a time e.g. cannot move from CKD3 to ESRD in one model cycle (month)
- Assumes no history of cardiovascular events – but [redacted] had myocardial infarction at baseline in OPAL-HK
- Bias in terms of from the 2nd cycle K+>6.0 not able to improve to K+<5.5
- Hyperkalaemia only recurs for a small proportion of people in model
  - model biased in favour of a short treatment period
  - when treatment stops costs are not incurred, but benefits of treatment remain for most

◉ *What are the implications of each of the ERG's concerns?*

[redacted]

Company updated analyses – an explanation

- **Company updated ACD response:** Company submitted updated base case in response to ACD, key changes = updated model
- **ERG** critiqued company updated base case and made adjustments (slide 26)
- **Company further response:** updated base case in response to ERG critique:
  - updated patient access scheme discount for patiromer
  - accepted most of the ERG's adjustments
  - updated population: people with serum potassium ≥6.0 mmol/L, OPAL-HK data limited n=[redacted] (slide 22)
  - updated treatment stopping curve: based on observational data (slide 28)
  - excluded a direct link between serum potassium and mortality

[redacted]

ERG adjustments to company base case

Company accepts all ERG changes in latest base case except 7 and adjusts 9
ERG agrees with company adjustment.

3) Correcting error in age-adjustment of quality of life values

4) Correcting error in monthly instead of annual costing for some events

5) Correcting error in probability of cardiovascular events

6) Absolute quality of life values: ERG applied cardiovascular event quality of life values as absolute values, instead of multiplicative approach

7) AMETHYST-DN time to discontinuation curve: Maximum treatment duration 5 years

8) Risk of hyperkalaemia related events: Assume risks for people on reduced RAASi dose are midway between no RAASi and full RAASi dose

9) Cost of patiromer: in first cycle (month) should be increased to account for people who did not continue to part B of OPAL-HK **243/107=2.27**
Company: accepts adjustment but makes changes to calculation: only people eligible for part B at baseline (141) should be included **141/107=1.32**
ERG: accepts this

[redacted]

Company updated base case: how long people take patiromer (1)

Major driver of cost-effectiveness results

- **Company**: Now uses observational US claims data, 2016 to 2019
- 1st meeting used data from AMETHYST-DN a dose ranging study of patiromer in adults with type 2 diabetes and CKD; 1 year follow-up
- Company did not use OPAL-HK because too short (16 weeks)
- **ERG:** Prefer to use AMETHYST-DN with maximum time on treatment of 5 years, provides scenario with OPAL-HK data

Company justification:

- Claims data more appropriate for compliance and persistence than trial data
- Claims data available for 3 years rather than just 1 year from AMETHYST-DN

ERG comment:

- US insurance claims data not representative of UK NHS resource use

Company updated base case: how long people take patiromer (2)

Company: 3 years US claims data most appropriate source of data (log-normal curve)

ERG uses AMETHYST-DN data (1 year) extrapolated using log-normal curve, treatment stops at 5 years

ERG scenario uses OPAL-HK data

ERG: All curves may overestimate stopping:

- curves are based on wider population than K+ >6.0mmol/L
- people with baseline K^+ >6.0mmol/L may stay on patiromer longer than people with K+ <6.0mmol/L

Company updated base case: how long people take patiromer (3)

	Proportion remaining on treatment		
	AMETHYST-DN	OPAL-HK	US claims data
1 month	[redacted]	[redacted]	[redacted]
1 year	[redacted]	[redacted]	[redacted]
3 years	[redacted]	[redacted]	[redacted]

ERG comments: US claims data mean duration [redacted]

- Discontinuation driven by differences in service setting, [redacted] of patients only receive [redacted] of patiromer
- Patient characteristics and reasons for discontinuation not presented
- **Model assumptions:** recurrence of severe hyperkalaemia and K^+>6.0mmol/L in the patiromer arm remains relatively low – model biased in favour of short treatment duration

ERG comments: OPAL-HK

- short trial period means extrapolation is uncertain

⊙ *Is it more appropriate to extrapolate treatment discontinuation based on US claims data, OPAL-HK or AMETHYST-DN data?*

Company cost effectiveness results with updated PAS, K+ >6.0mmol/L

	Deterministic			Probabilistic ICER
	Inc cost	Inc QALYs	ICER £/QALY	
Patiromer vs. usual care	£118	0.026	£4,510	£6,774

[redacted]

ERG cost effectiveness results with updated PAS, K+ >6.0mmol/L

Patiromer vs. usual care	Deterministic analyses		
	Inc cost	Inc QALYs	ICER (£/QALY)
Company base case	£118	0.026	**£4,510**
ERG base case: stopping based on AMETHYST-DN, everyone stops at year 5	£4,232	0.018	**£232,000**
ERG scenario: stopping based on OPAL-HK	£663	0.025	**£26,353**

Using AMETHYST-DN curve has significant effect on the cost effectiveness estimate because:

- Around [redacted] of patients are on treatment at 3 years vs [redacted] using company's preferred data source
- Incremental costs in ERG analysis are £4,232 vs. £118 in company base case for the same population

[redacted]

Key Issues

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  - is this reasonable?
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- Regarding how long people continue to take patiromer, company chooses not to use trial data but instead use US observational data. Which is more appropriate?
- Is patiromer innovative?
- Any equality issues?

[redacted]