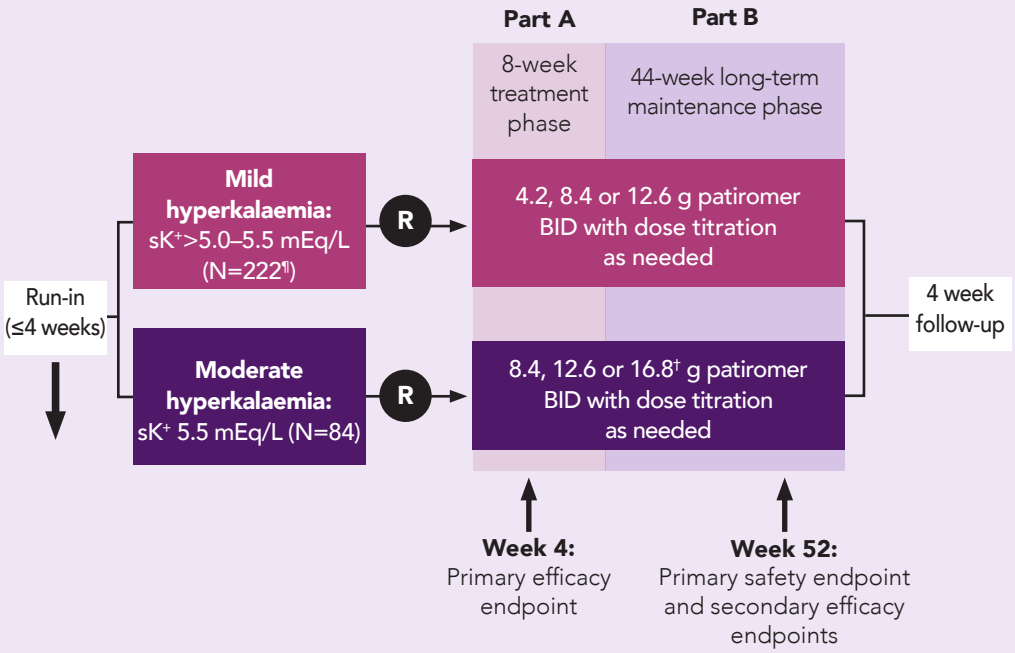
AMETHYST-DN STUDY

AMETHYST-DN: long-term safety and efficacy of patiromer for management of hyperkalaemia in patients with hypertension and diabetic nephropathy

STUDY DESIGN

Phase 2, **52-week**, multicentre, open-label, **dose-ranging study** in 306 outpatients with T2DM

Inclusion criteria: CKD*, T2DM, stable RAASi dose ≥4 weeks AND ACR ≥30 mg/g with sK^+ 4.3–5.0 mEq/L (Cohorts 1 and 2) OR sK^+ >5.0–<6.0 mEq/L (Cohort 3)



Primary efficacy endpoint

Mean change in serum potassium level from baseline to Week 4 or prior to initiation of dose titration

Key secondary efficacy endpoint

Mean change in serum potassium level through 52 weeks

Primary safety endpoint

Adverse events through 52 weeks

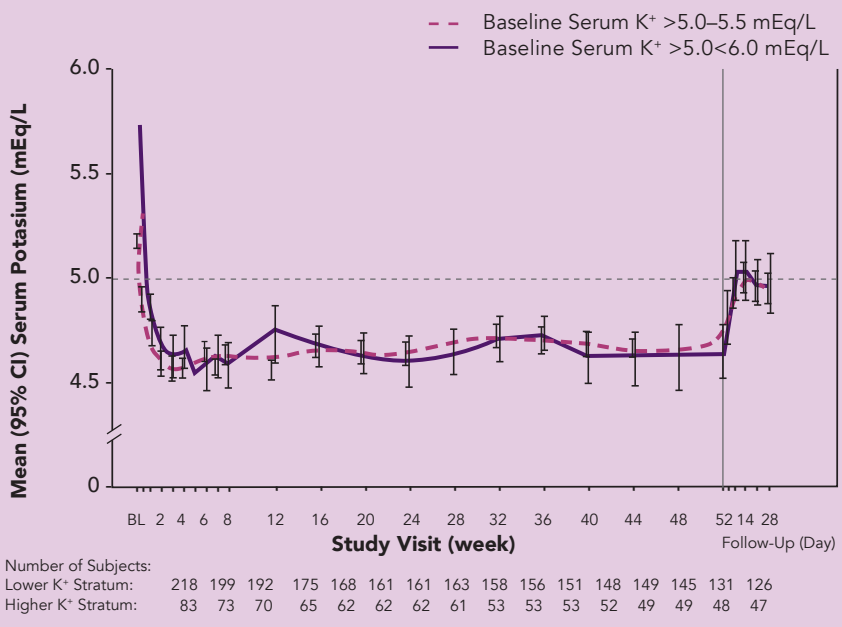
Cohort 1: Discontinue RAASi, start losartan 100 mg/day, add spironolactone after Week 2 if required; **Cohort 2**: Maintain RAASi, start spironolactone 25 mg/day; **Cohort 3**: Skip run-in and maintain current RAASi*

*eGFR 15–60 mL/min/m^2; † Dose studied but not registered. ¶ Two patients with mild hyperkalaemia did not receive patiromer and therefore were not included in the efficacy or safety analyses.

RESULTS

In patients with mild and moderate hyperkalaemia, **significant reductions in sK^+** were observed after 4 weeks of treatment with patiromer, and maintained through 52 weeks in:

- **83.1% to 92.7% of patients with mild hyperkalaemia**
- **77.4% to 95.1% of patients with moderate hyperkalaemia**



AMETHYST-DN STUDY

RESULTS

Among treatment related adverse events, the most frequently reported were:

hypomagnesaemia	constipation	diarrhoea
7.2%*	**4.6%**	**2.7%**

Hypokalaemia (sK^+<3.5 mEq/L) occurred in 17 patients (5.6%), with no patients developing a sK^+ level <3.0 mEq/L.

Reductions in systolic and **diastolic blood pressure** were observed in all starting-dose groups in both strata over 52 weeks

Mean SBP/DBP	**Mild hyperkalaemia**	**Moderate hyperkalaemia**
Baseline	153.5/83.6 mmHg	153.8/81.9 mmHg
Reduction from baseline to Week 52	-15.7/-8.0 mmHg	-17.1/9.2 mmHg

*No patients developed severe hypomagnesaemia (<1.0 mg/dL)

CONCLUSIONS

AMETHYST-DN showed that in patients with hyperkalaemia and diabetic nephropathy

patiromer starting doses of **4.2** to **16.8 g** BID → resulted in statistically significant **decreases in sK^+ level** → after 4 weeks of treatment lasting through **52 weeks**

The study data demonstrate the long-term efficacy and safety of patiromer in patients with hypertension and diabetic nephropathy

The recommended starting dose is 8.4 g patiromer once daily[2]

Abbreviations: ACR, albumin creatinine ratio; BID, twice daily; BL, baseline; CKD, chronic kidney disease; DN, diabetic nephropathy; eGFR, estimated glomerular filtration rate; K^+, potassium; R, randomisation; RAASi, renin-angiotensin-aldosterone system inhibitor; sK^+, serum postassium; T2DM, type 2 diabetes mellitus.

*Patients who developed hyperkalaemia at any time during the 4-week run-in were eligible to be randomised into the treatment phase

1. Bakris GL, *et al.* Effect of patiromer on serum potassium level in patients with hyperkalemia and diabetic kidney disease: The AMETHYST-DN Randomized Clinical Trial *JAMA.* 2015;314(2):151–61.

2. European Medicines Agency. Veltassa. Summary of Product Characteristics. Available at: https://www.ema.europa.eu/en/documents/product-information/veltassa-epar-product-information_en.pdf. Accessed September 2019.

VIFOR PHARMA

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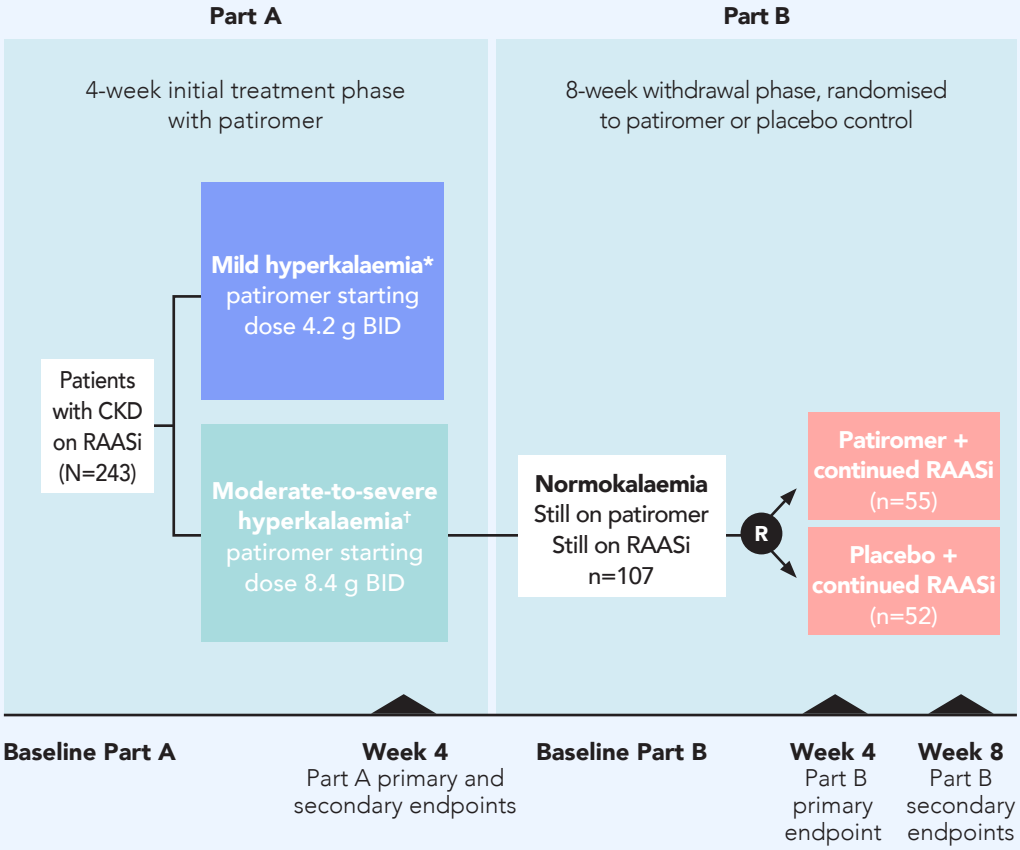
OPAL-HK STUDY

Efficacy and safety of patiromer for the treatment of hyperkalaemia in patients with CKD receiving RAASi[1]

STUDY DESIGN

Inclusion criteria: patients with stage 3–4 CKD (eGFR <60mL/min/m^2) with hyperkalaemia (sK$^+$ 5.1 to <6.5 mEq/L) using RAASi



Comorbidities/treatments at baseline: CKD (100%), HF (42%), T2DM (57%), hypertension (97%), RAASi (100%)
*Mild hyperkalaemia defined as baseline sK$^+$ 5.1 to <5.5 mEq/L; †Moderate-to-severe hyperkalaemia defined as baseline sK$^+$ 5.5 to <6.5 mEq/L

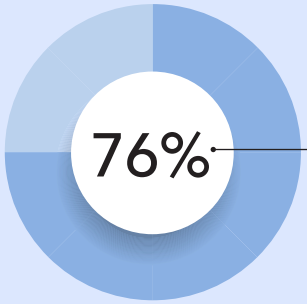
RESULTS

4-week initial treatment phase outcomes

Primary endpoint:

Patiromer treatment significantly reduced elevated sK$^+$ levels

–1.01 mEq/L mean change from baseline to Week 4



Secondary endpoint:

76% of patients treated with patiromer had sK$^+$ in target range at Week 4

OPAL-HK STUDY

RESULTS

8-week randomised withdrawal phase outcomes

Patiromer maintained **normal sK⁺ levels**

sK⁺ levels increased with placebo (between-group difference of 0.72 mEq/L)

Reduced RAASi dose due to hyperkalaemia*

Patiromer (**6%**)
Placebo (**66%**)

*At least one sK+ level ≥5.5 mmol/L

Discontinued RAASi due to hyperkalaemia

Patiromer (**6%**)
Placebo (**56%**)

Patients on RAASi

Patiromer (**94%**)
Placebo (**44%**)

Safety

Most common adverse event: mild-to-moderate constipation (11% during initial treatment; 4% during randomised withdrawal phase)

This generally **did not** limit treatment with patiromer

The rates of all other adverse events with patiromer were low and similar to those with placebo in the randomised withdrawal phase

CONCLUSIONS

OPAL-HK demonstrated that patiromer...

...provides significant and clinically meaningful sK⁺ reduction → ...maintains normal K⁺ levels → ...and has the ability to keep patients on RAASi medications

Recurrence of hyperkalaemia upon treatment withdrawal demonstrates the need for long-term treatment

Abbreviations: BID, twice a day; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HF, heart failure; RAASi, renin–angiotensin–aldosterone system inhibitors; sK⁺, serum K⁺; T2DM, type 2 diabetes mellitus.

1. Weir MR *et al.* Patiromer in patients with kidney disease and hyperkalemia receiving RAAS inhibitors. *N Engl J Med* 2015;372:211–21.

VIFOR PHARMA

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PEARL-HF STUDY

Evaluating the efficacy and safety of patiromer for control of sK^+ levels in patients with chronic heart failure (CHF) receiving standard therapy and spironolactone[1]

STUDY DESIGN

28-day double-blind, randomised, placebo-controlled, parallel-group study of patiromer in:

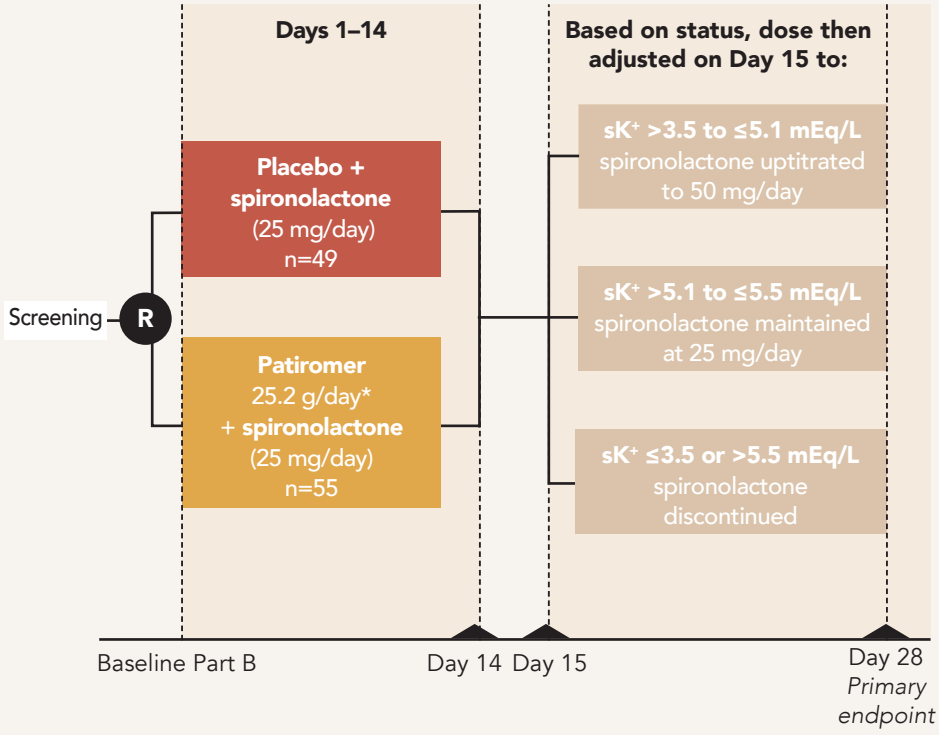
104 adults (age 18+ years) with CHF clinically indicated to receive spironolactone and sK^+ 4.3–5.1 mEq/L:

AND

- having CKD (eGFR <60 mL/min) and on ≥1 RAASi or BB

OR

- documented hyperkalaemia that led to discontinuation of RAASi or BB within 6 months



*fixed-dose (no dose titration permitted)

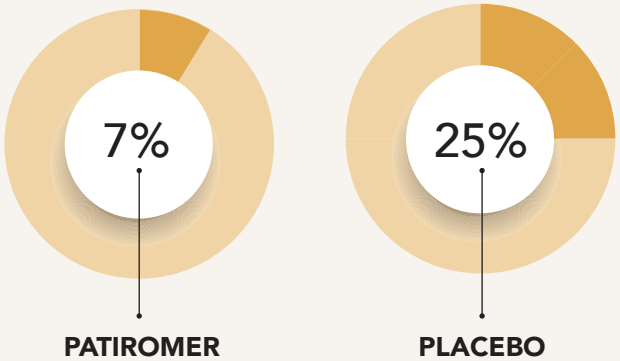
RESULTS

Primary efficacy endpoint

End-of-treatment between-group difference = –0.45 mEq/L (P<0.001)

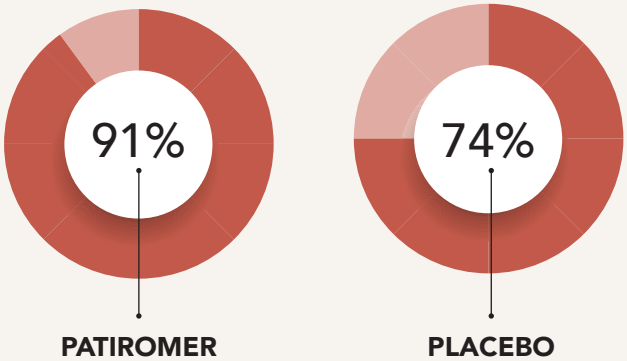
Patiromer significantly lowered sK^+ levels compared with placebo

At end of treatment (Day 28) incidence of hyperkalaemia was significantly lower with patiromer versus placebo:*



*P=0.015; hyperkalaemia defined as >5.5 mEq/L

Proportion of patients up-titrated to spironolactone 50 mg/day was significantly higher with patiromer versus placebo:



PEARL-HF STUDY

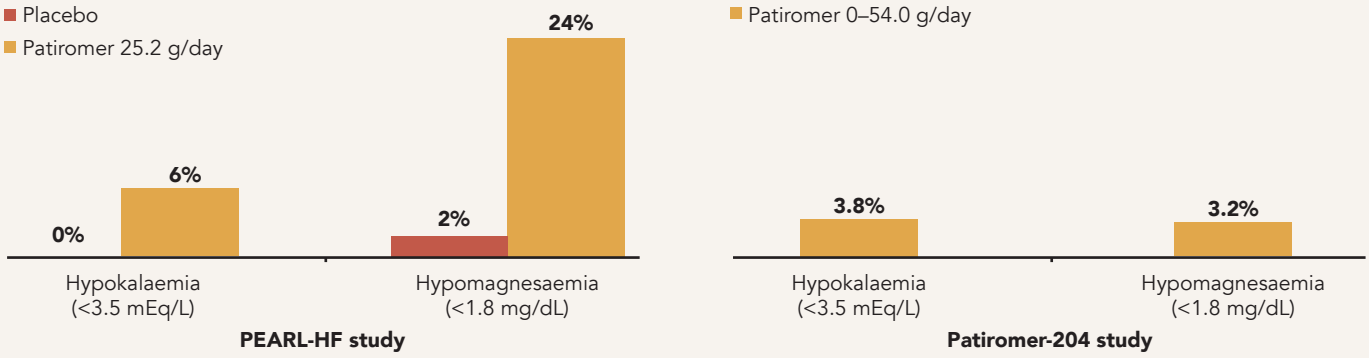
RESULTS

Safety

Patiromer was relatively well tolerated over the 4-week study

Incidence of hypokalaemia and hypomagnesaemia was higher with patiromer versus placebo, and likely due to the fixed-dose strategy used in PEARL-HF

In a subsequent trial (Patiromer-204 study), which evaluated an individualised dose titration regimen of patiromer for prevention of hyperkalaemia in a similar population (i.e. patients with HF and CKD initiating spironolactone), lower rates of hypokalaemia and hypomagnesaemia were reported, when dose titration was permitted[2]



CONCLUSIONS

PEARL-HF demonstrated that in normokalaemic patients with CHF at risk of HK who had started spironolactone therapy, administration of patiromer...*

...significantly reduced mean sK^+ levels

...prevented hyperkalaemia

...allowed more patients to increase spironolactone dosage to 50 mg/day

*compared with placebo

European Society of Cardiology consensus recommendation[3]:
Patiromer and SZC may be considered in patients with HF with or without CKD, to manage hyperkalaemia, and may enable the use of RAASis in more patients and at higher doses

Abbreviations: BB, beta blockers; BID, twice a day; CHF, chronic heart failure; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HF, heart failure; HK, hyperkalaemia; RAASi, renin–angiotensin–aldosterone system inhibitor; sK^+, serum K^+; SZC, sodium zirconium cyclosilicate.

1. Pitt B *et al*. Evaluation of the efficacy and safety of RLY5016, a polymeric potassium binder, in a double-blind, placebo-controlled study in patients with chronic heart failure (the PEARL-HF) trial *Eur Heart J* 2011;32:820–8.
2. Pitt B *et al*. Evaluation of an individualized dose titration regimen of patiromer to prevent hyperkalaemia in patients with heart failure and chronic kidney disease *ESC Heart Fail* 2018;5: 257–66.
3. Seferovic P *et al*. Clinical practice update on heart failure 2019: pharmacotherapy, procedures, devices and patient management. An expert consensus meeting report of The Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* 2019; doi: 10.1002/ejhf.1531. [Epub ahead of print]

VIFOR PHARMA

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AMBER STUDY

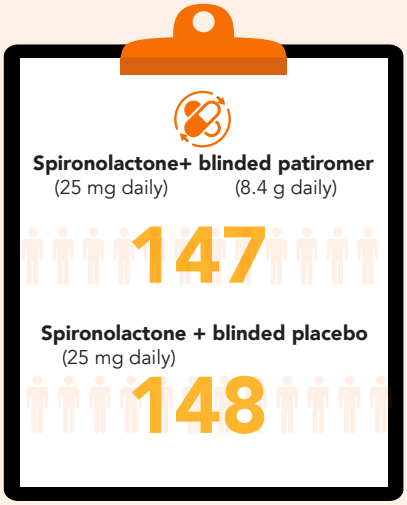
Evaluating whether patiromer can enable persistent use of spironolactone in patients with rHTN and advanced CKD, by managing hyperkalaemia

Spironolactone is an effective treatment for rHTN*, but many previous studies have excluded patients with advanced CKD (eGFR <45 mL/min/1.73 m^2) who are at high risk of hyperkalaemia;[1] **AMBER** is the first study to evaluate whether patiromer can enable spironolactone use in this patient population.

*rHTN: blood pressure above goal despite adherence to a combination of at least 3 optimally dosed antihypertensive medications, one of which is a diuretic

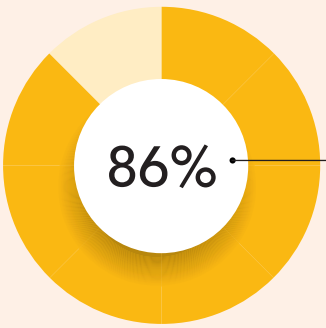
295 patients with **rHTN** and advanced **CKD**
- Systolic AOBP 135–160 mmHg
- eGFR 25–45 mL/min/1.73 m^2

randomised 1:1 to

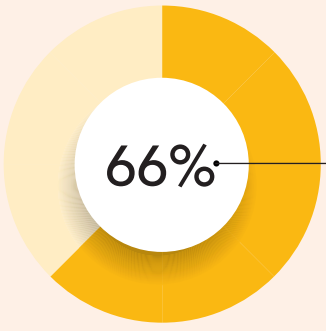


PRIMARY ENDPOINT

In advanced CKD with rHTN, patiromer enables more persistent use of spironolactone
Primary endpoint: between-group difference in % of patients who remained on spironolactone at week 12:

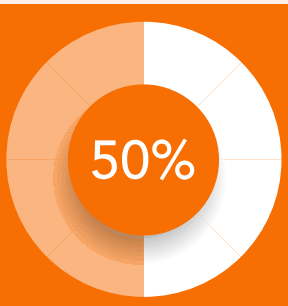


PATIROMER



PLACEBO

Among patients receiving placebo,
2 out of 3 developed hyperkalaemia.



Patiromer reduced this **risk by half.**

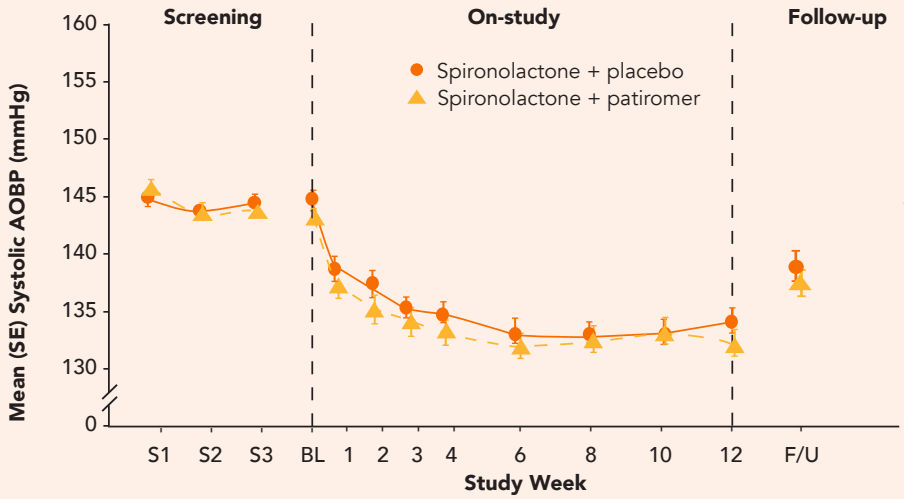
AMBER STUDY

SECONDARY ENDPOINT

Secondary endpoint: between-group difference in change of systolic BP at **week 12**

Spironolactone use in patients with advanced CKD and rHTN resulted in a clinically significant 11–12 mmHg reduction in systolic BP, with a difference between groups of –1 mmHg, P=0.58

SYSTOLIC AOBP OVER TIME



Spironolactone metabolites were detectable long after discontinuation* and with the long half-lives of spironolactone metabolites, approximately half of the systolic BP effect was still present, 2 weeks after discontinuation of spironolactone.

As most discontinuations in the placebo group occurred after 6 weeks of the study; it may be possible that there was insufficient time to observe a difference in systolic AOBP between treatment groups.

* in 36.4% of patients 3 weeks after discontinuation of spironolactone

These findings are noteworthy because meta-analyses of RCTs have shown that a 10 mmHg drop in systolic blood pressure could mean[2,3]

↓20%	↓20%	↓40%	↓10–15%	↓35%
major CV events	coronary events	heart failure	all-cause mortality	stroke

Patiromer's safety profile was consistent with previous reports[4–6]

Abbreviations: AOBP, automated office blood pressure; BL, baseline; BP, blood pressure; CKD, chronic kidney disease; CV, cardiovascular; eGFR, estimated glomerular filtration rate; F/U, follow-up; RCT, randomised controlled trial; rHTN, resistant hypertension; SE, standard error

1. Williams B *et al.* Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2): a randomised, double-blind, crossover trial. *Lancet* 2015;386:2059–2068.
2. Ettehad D *et al.* Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. *Lancet* 2016;387:957–967.
3. Thomopoulos C *et al.* Effects of blood pressure lowering on outcome incidence in hypertension. 1.Overview, meta-analyses, and meta-regression analyses of randomized trials. *J Hypertens* 2014;32:2285–2295.
4. Weir MR *et al.* Patiromer in patients with kidney disease and hyperkalemia receiving RAAS inhibitors. *N Engl J Med* 2015;372:211–221.
5. Bakris GL *et al.* Effect of patiromer on potassium level in patients with hyperkalemia and diabetic kidney disease: the AMETHYST-DN randomized clinical trial. *JAMA* 2015;314:151–161.
6. Pitt B *et al.* Evaluation of the efficacy and safety of RLY5016, a polymeric potassium binder, in a double-blind, placebo-controlled study in patients with chronic heart failure (the PEARL-HF) trial. *Eur Heart J* 2011;32:820–828.

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