Un nouveau traitement de l'hyperkaliémie pour optimiser l'utilisation des bloqueurs du SRAA

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Disclosures

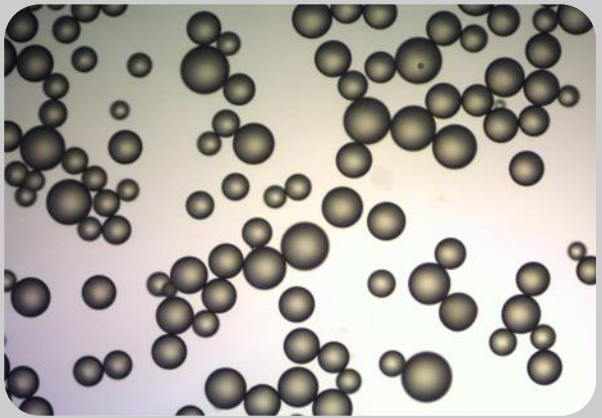
- **consultant:** AstraZeneca, Bayer, CTMA, CVRx, Daiichi Sankyo, Fresenius, Gambro, G3P, Grünenthal, H.A.C. Pharma, Novartis, **Relypsa**, Sanofi, Servier, Stealth Peptides, **Vifor Fresenius Medical Care Renal Pharma, Vifor**
- **Research grants:** AstraZeneca, BG Medicine, BMS, **Relypsa**, Roche, **Vifor Fresenius Medical care**
- **Travel grants:** AstraZeneca, Bayer, Daiichi Sankyo, Gambro, Novartis, Servier, Vifor and Takeda
- CardioRenal co-founder

Properties of patiromer

Patiromer

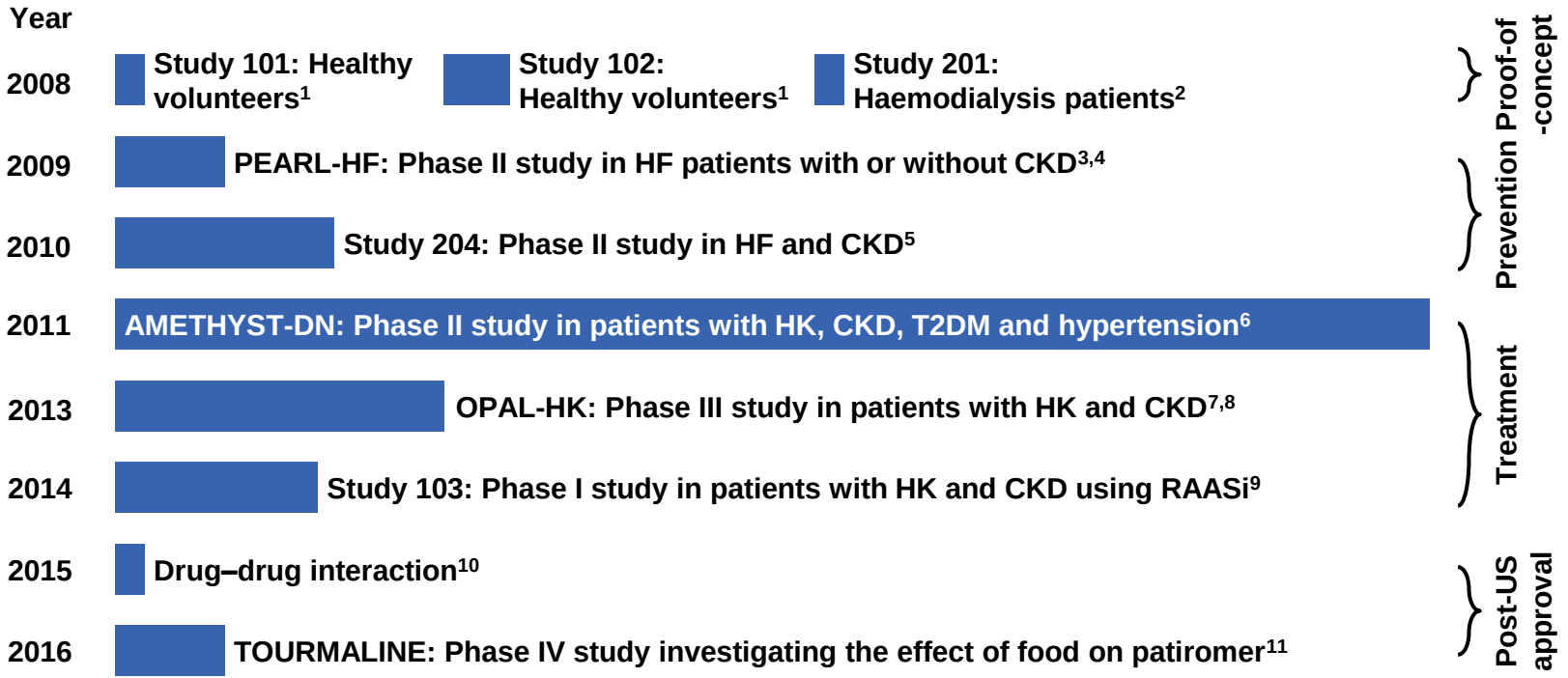
- **Organic potassium binder[1]**
- **Orally administered[1]**
- **Non-absorbed[1]**
- **Calcium-exchange polymer that binds potassium and increases potassium excretion[1]**

Electron microscopy image[2]



1. Buysse J *et al*. *Future Cardiol* 2012;8:17–28; 2. Cope J *et al*. Presented at*:* American Society of Nephrology Renal Week; Denver, CO; Nov 16–21, 2010. Poster F-PO1616

Patiromer clinical programme



1. Huang I-Z *et al*. *J Am Soc Nephrol* 2010;21(Suppl):482A; 2. https://clinicaltrials.gov/ct2/show/NCT02033317. Accessed June 2017; 3. Pitt B *et al*. *Eur Heart J* 2011;32:820–8; 4. Buysse J *et al*. *Future Cardiol* 2012;8(1):17–28; 5. https://clinicaltrials.gov/ct2/show/study/NCT01130597. Accessed June 2017; 6. Bakris GL *et al*. *JAMA* 2015;314:151–61; 7. Weir M *et al*. *N Engl J Med* 2015;372:211–21; 8. Weir M *et al.* Presented at: Am Soc of Hypertension 2015; LB-P-01; 9. Bushinsky DA *et al. Kidney Int* 2015;88:1427–33; 10. Lesco LJ *et al. J Cardiovasc Pharmacol Ther* 2017;ePub ahead of print; 11. https://clinicaltrials.gov/ct2/show/NCT02694744. Accessed June 2017

Patiromer in patients using RAASi

AMETHYST-DN

1-year, Phase II, open-label, randomized, dose-ranging efficacy and safety study in patients with CKD including a RAASi run-in period for patients who needed RAASi to control their blood pressure

Bakris GL *et al*. *JAMA* 2015;314:151–61

OPAL-HK

Two-part, 12-week, Phase III, single-blind randomized withdrawal study in patients with HK and CKD, using at least one RAASi at a stable dose

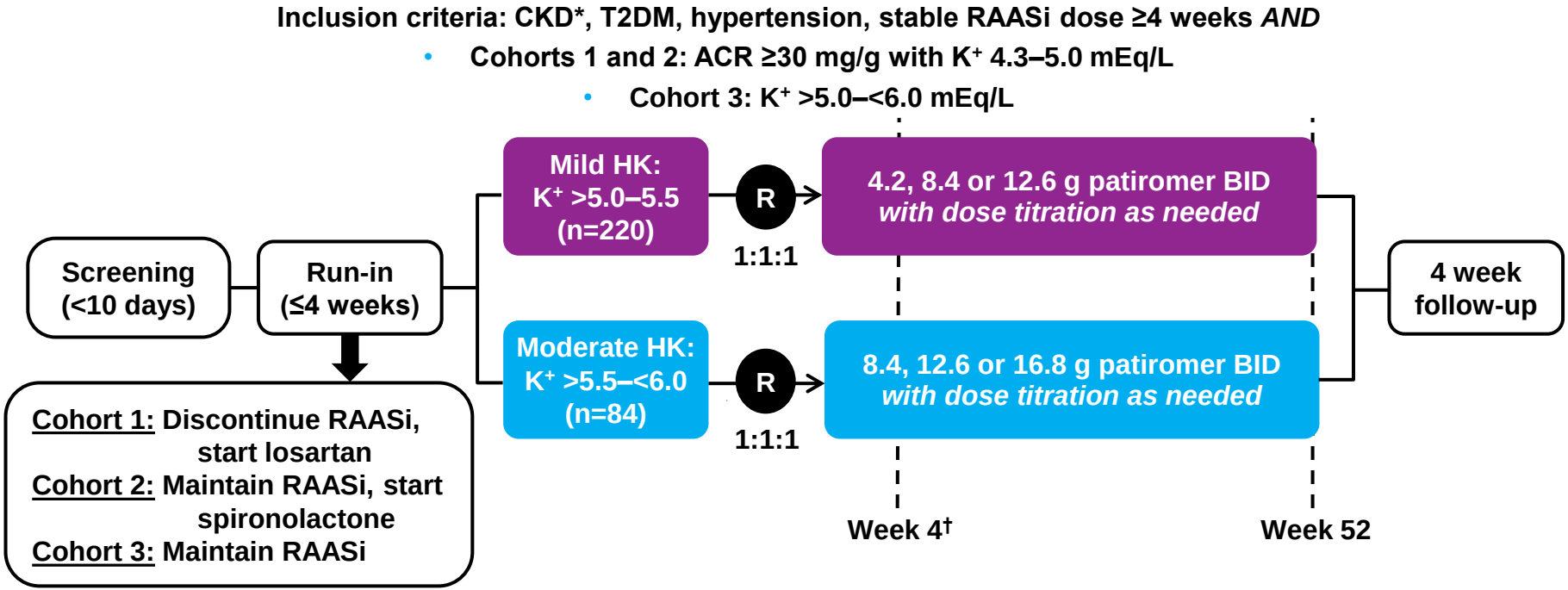
Weir M *et al*. *N Engl J Med* 2015;372:211–21

PEARL-HF

28-day, Phase II, randomized, double-blind, placebo-controlled, parallel-group study in HF patients at high risk for HK and initiating spironolactone

Pitt B *et al*. *Eur Heart J* 2011;32:820–8

AMETHYST-DN: Phase II, 52-week, open-label study



*eGFR 15–60 mL/min/m^2; †Primary endpoint

ACR, albumin creatinine ratio; BID, twice weekly; HTN, hypertension

Bakris GL *et al. JAMA* 2015;314:151–61

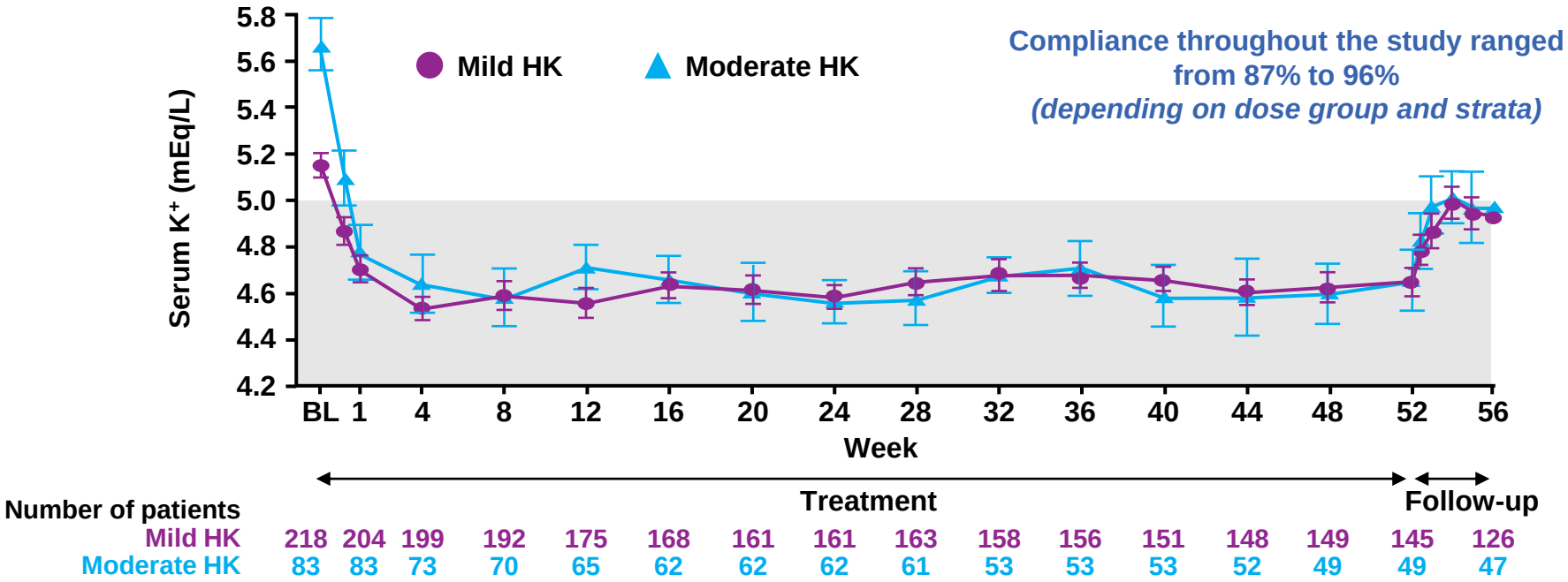
AMETHYST-DN: Baseline demographic characteristics

	Mild HK (n=220)	Moderate HK (n=84)
Male, %	**63**	**63**
Mean age, yrs (SD)	**66.5 (8.8)**	**65.8 (8.2)**
White, %	**100**	**100**
Mean eGFR, mL/min/1.73 m^2 (SD)	**42 (15)**	**36 (16)**
CKD stage, n (%)		
3a	**68 (31)**	**17 (20)**
3b	**84 (38)**	**27 (32)**
4	**39 (1)**	**27 (32)**
5	**2 (1)**	**4 (5)**
Mean urine ACR, mg/g (SD)	**1124 (1901)**	**1217 (1666)**
HF, n (%)	**77 (35)**	**28 (33)**
Mean serum K^+, mEq/L (SD)	**5.2 (0.25)**	**5.7 (0.36)**
Mean sitting BP, mmHg (SD)		
Systolic	**155.1 (11.2)**	**156.5 (13.8)**
Diastolic	**84.4 (10.9)**	**82.9 (12.5)**

BP, blood pressure; SD, standard deviation; yrs, years

Bakris GL *et al*. *JAMA* 2015;314:151–61

AMETHYST-DN: Change in serum potassium levels

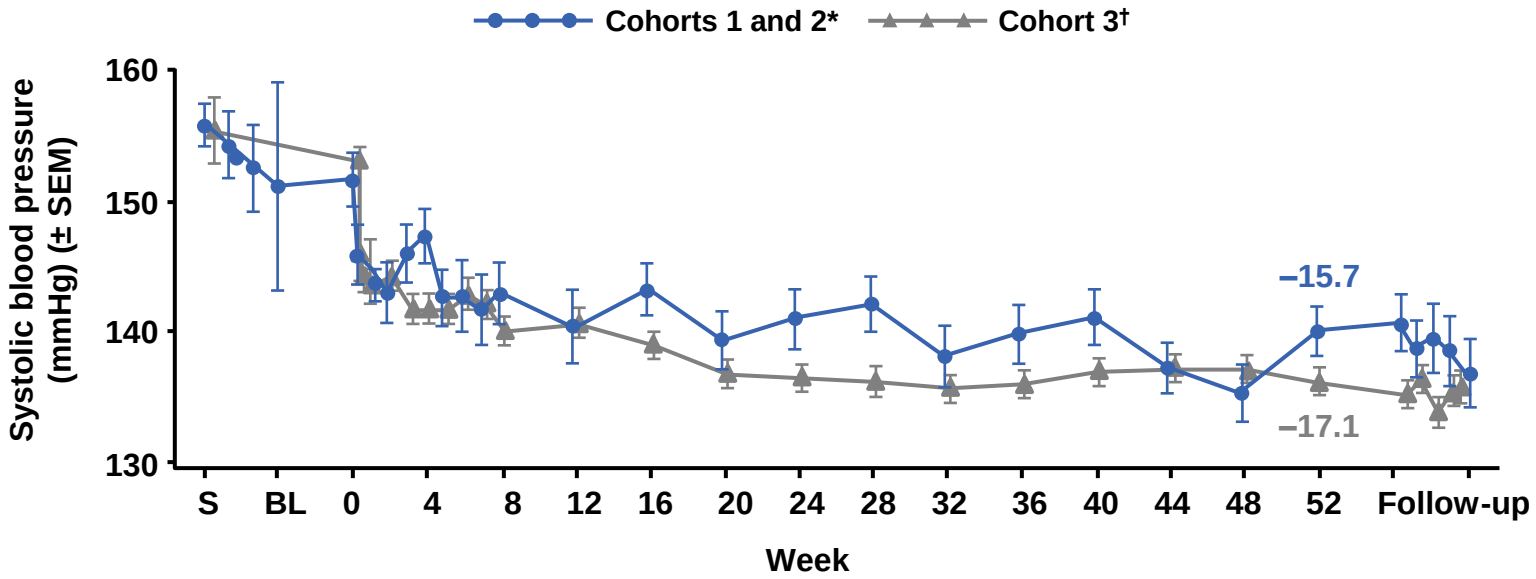


All serum potassium analyses are based on central lab values; 3 patients (2 with mild HK and 1 with moderate HK) did not have a central lab serum K^+ value at baseline and therefore are not included in the analysis at this timepoint; at all timepoints, $P<0.001$ (2-sided t-test) for lease squares mean changes from baseline and week 52 (or from last dose of patiromer received during the study. BL, baseline

Bakris G *et al*. *JAMA* 2015;314:151–61

AMETHYST-DN: Change in systolic blood pressure

- **Clinically relevant reductions in systolic blood pressure were observed in all starting dose groups in both strata**



*Cohort 1: Discontinue RAASi, start losartan, cohort 2: Maintain RAASi, start spironolactone; †Cohort 3: Maintain RAASi. S, screening

Epstein M *et al.* Presented at ERA-EDTA 2016: Abstract SO010

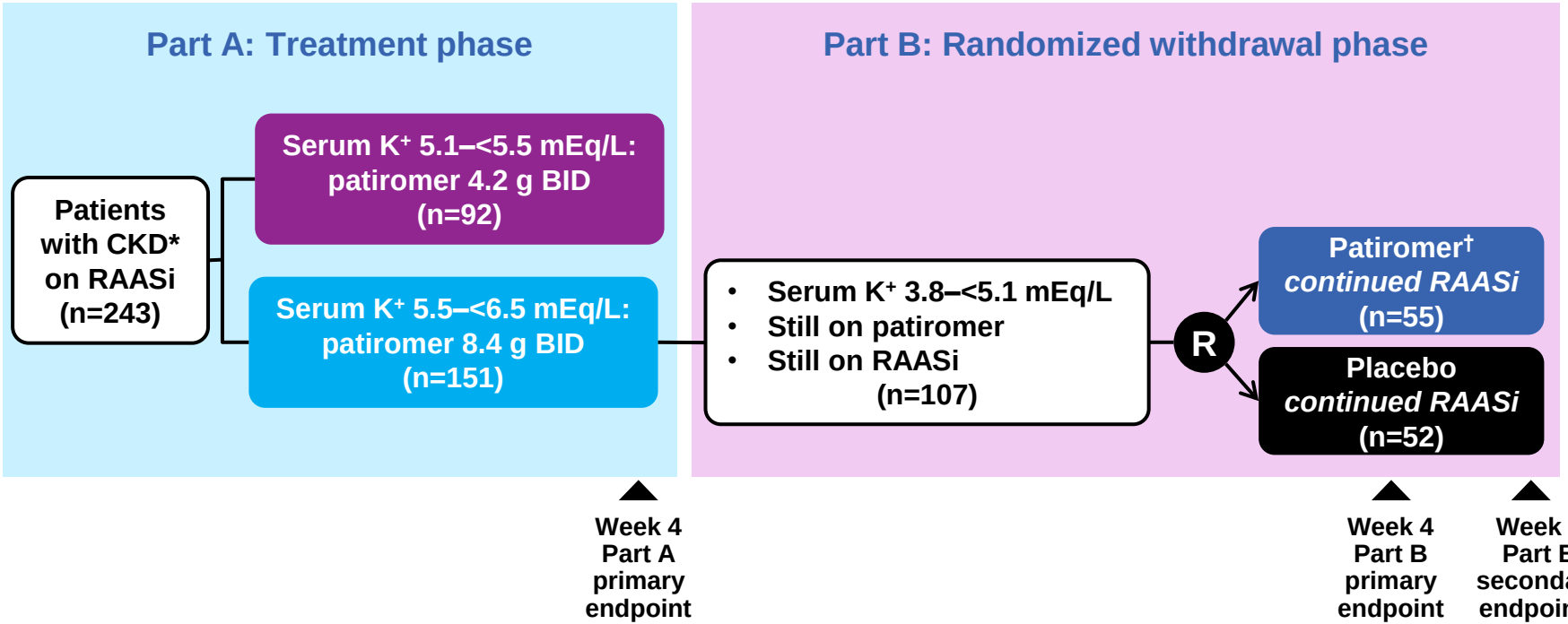
AMETHYST-DN: Most common AEs over 52 weeks*

AEs, n (%)	Mild HK (n=220)	Moderate HK (n=84)	Overall (n=304)
Hypomagnesaemia†	15 (7)	11 (13)	26 (9)
Worsening of hypertension	14 (6)	10 (12)	24 (8)
Worsening of CKD	14 (6)	14 (17)	28 (9)
Diarrhoea	12 (6)	5 (6)	17 (6)
Constipation	11 (5)	8 (10)	19 (6)
Hypoglycaemia†	4 (2)	6 (7)	10 (3)

*Occurring in ≥5.0% of patients in either baseline HK group; †Based on PI assessment; may not have correlated with lab values <LLN. LLN, lower limit of normal

Bakris GL *et al*. *JAMA* 2015;314:151–61

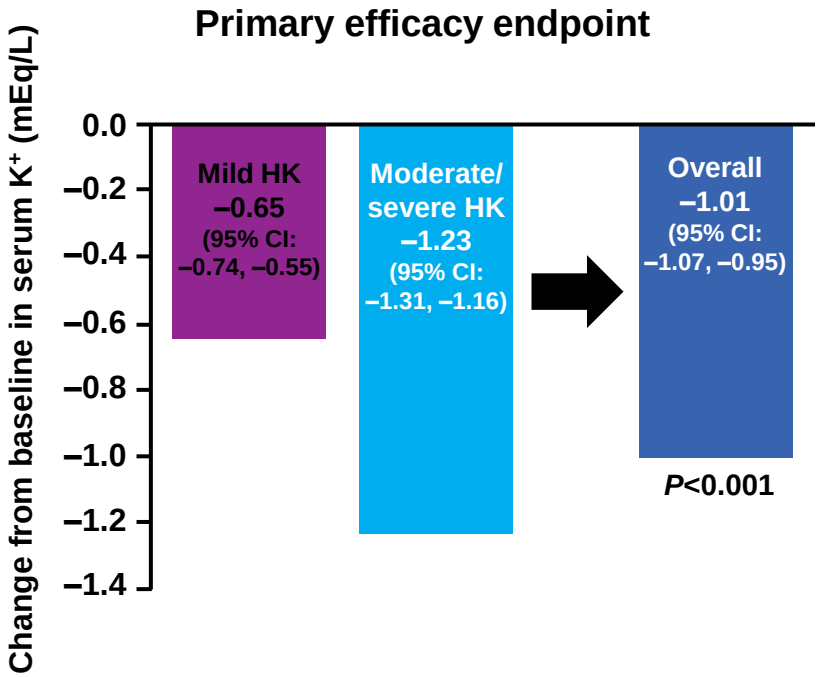
OPAL-HK: Phase III, 2-part, single-blind withdrawal study

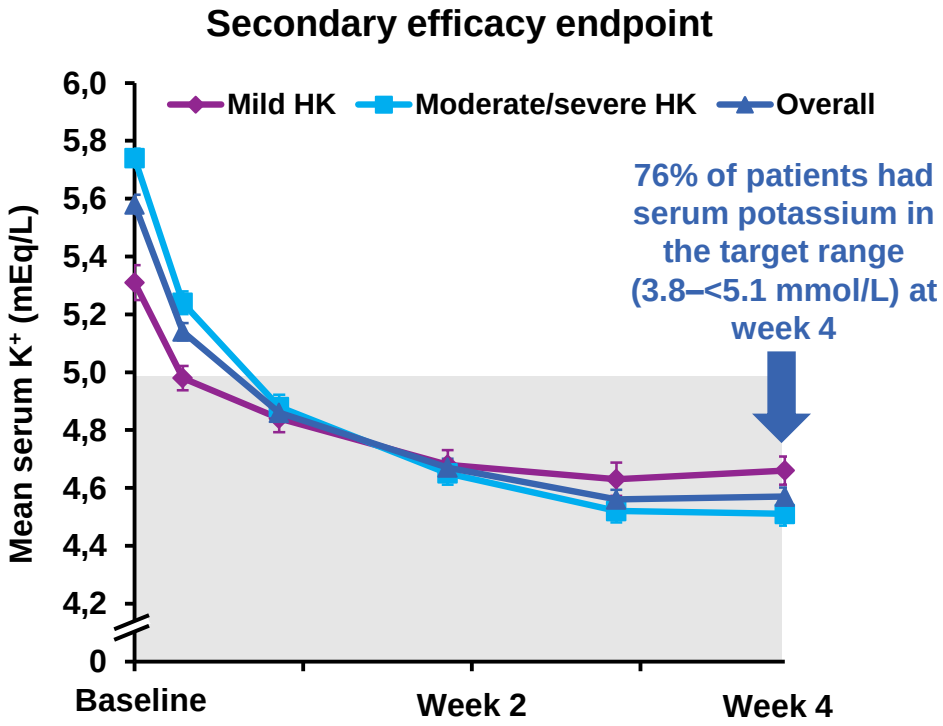


*eGFR 15 to <60 mL/min/m^2;
†Dose adjusted as needed by treating physician

1. Weir MR *et al*. *N Engl J Med* 2015;372:211–21; 2. Pitt B *et al*. Presented at: 18th Annual Scientific Meeting of the Heart Failure Society of America; Las Vegas, NV; Sept 14–17, 2014

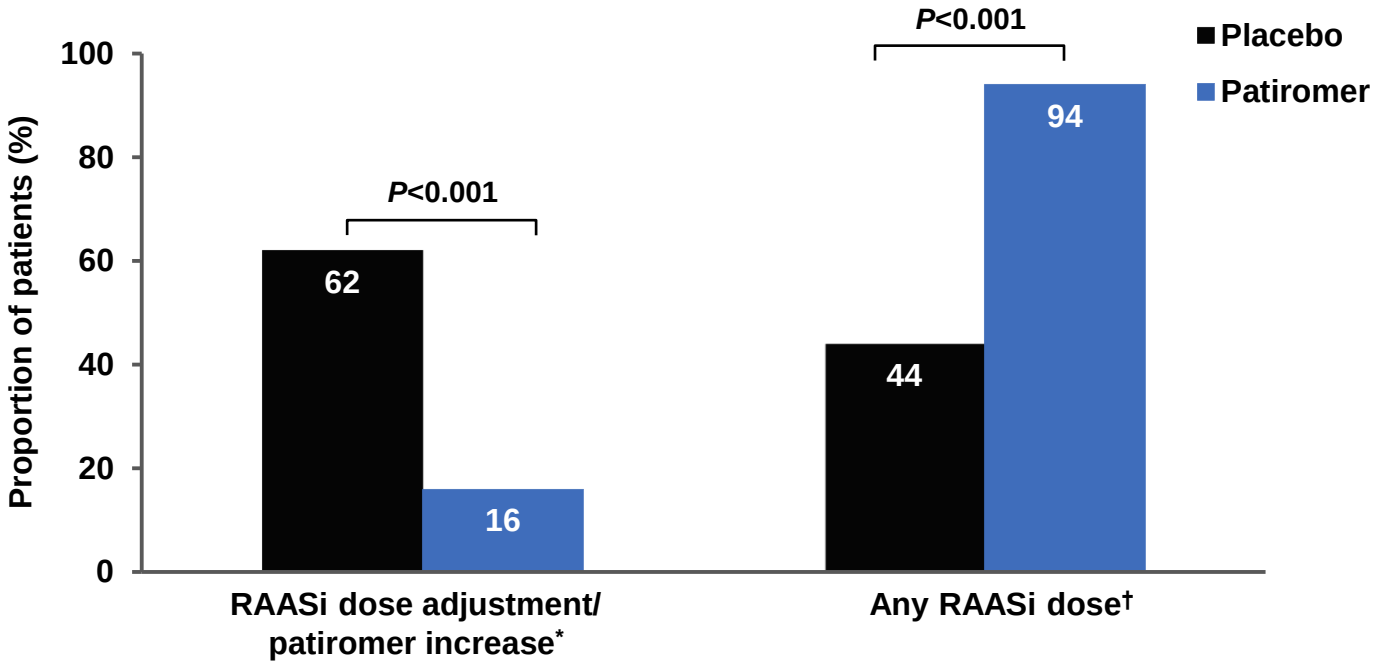
OPAL-HK (Part A): Primary and secondary efficacy endpoints





Weir MR *et al*. *N Engl J Med* 2015;372:211–21

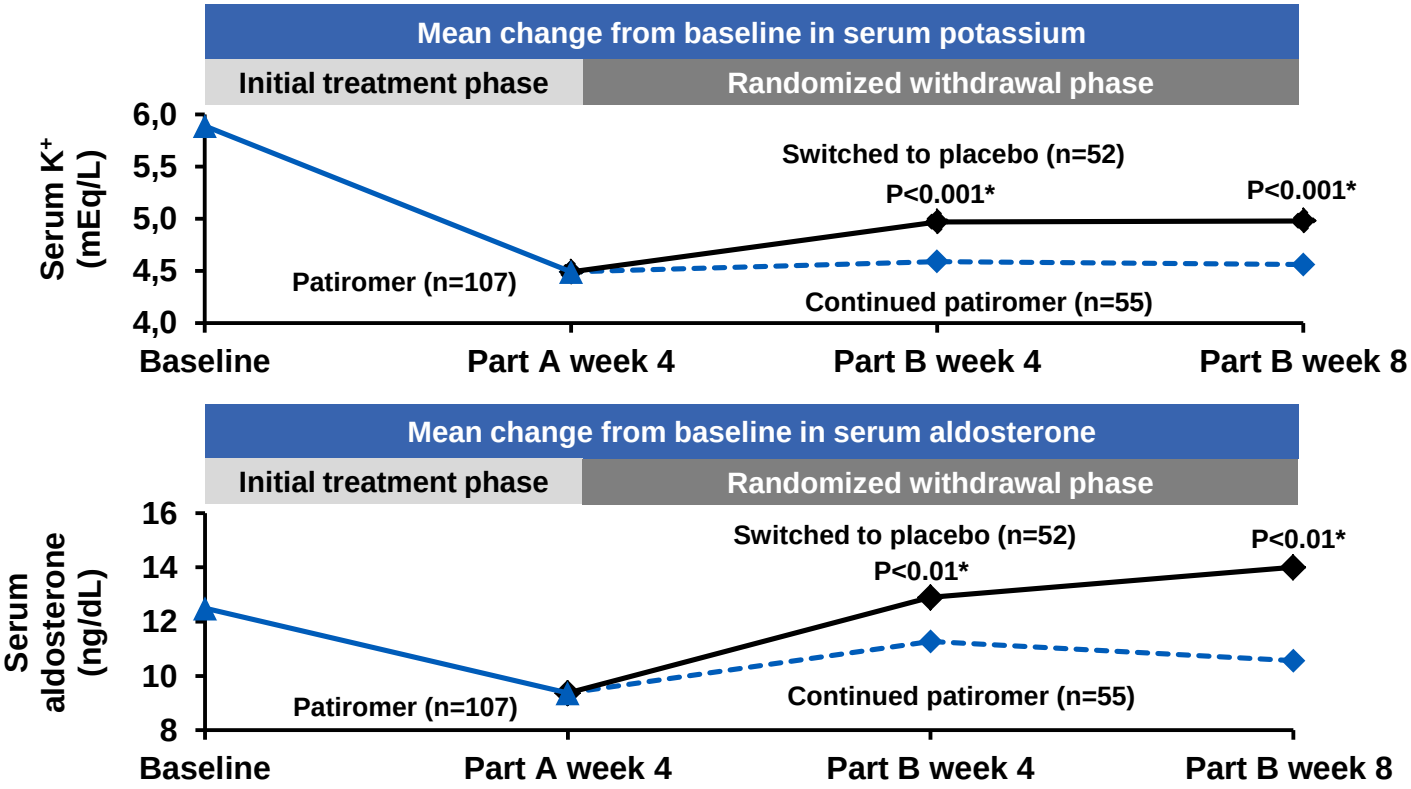
OPAL-HK (Part B): Exploratory endpoints – statistically significant results



*Requiring any adjustment of RAASi (ie down-titration or discontinuation) or patiromer dose increase due to hyperkalaemia at any time during Part B; †Receiving any dose of a RAASi at the end of Part B

Weir MR *et al*. *N Engl J Med* 2015;372:211–21

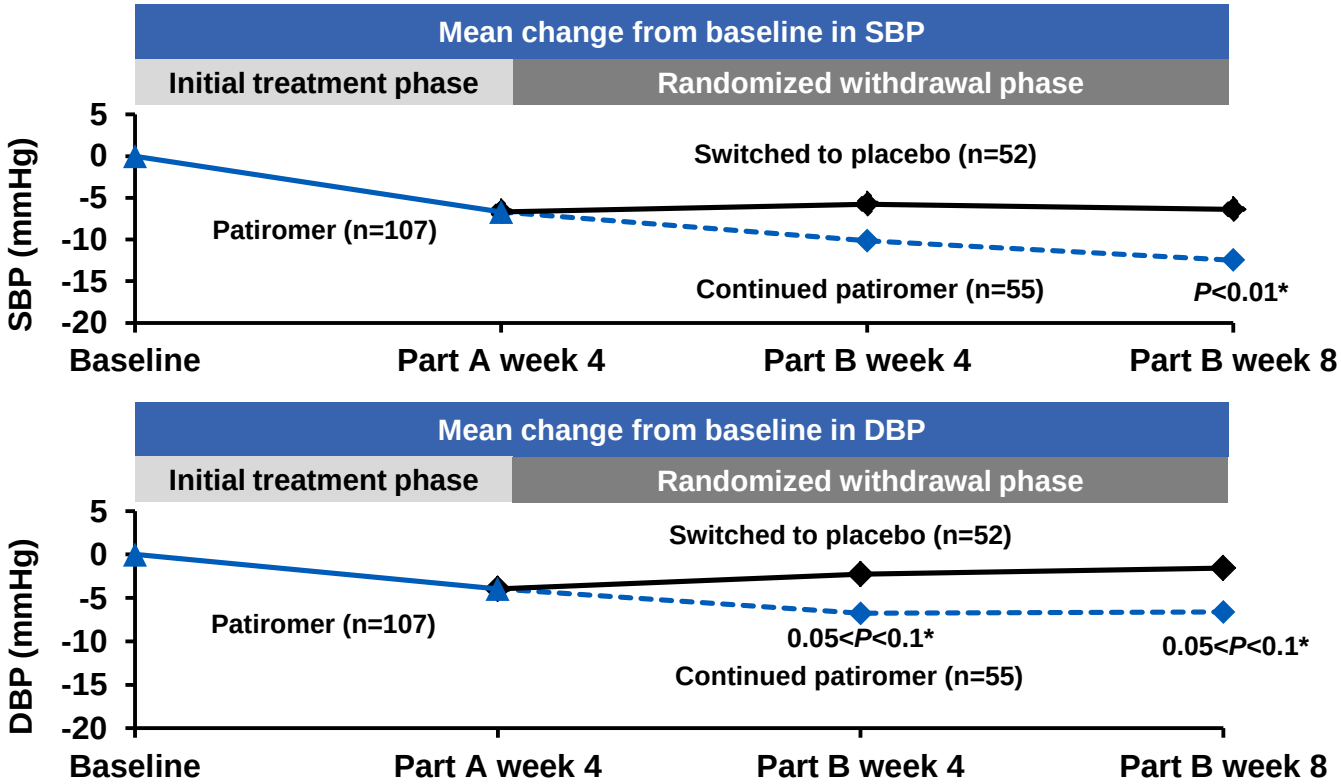
OPAL-HK (Part B): Serum potassium and aldosterone



*versus Part A Week 4

Weir MR *et al*. Presented at: Am Soc of Hypertension 2015; LB-P-01

OPAL-HK (Part B): Blood pressure



*versus Part A Week 4

Weir MR *et al*. Presented at: Am Soc of Hypertension. 2015; LB-P-01

OPAL-HK: Most common adverse events

Part A: Initial treatment phase*

AEs, n (%)	Patiromer (n=243)
Any	114 (47)
Constipation	26 (11)
Diarrhoea	8 (3)
Hypomagnesaemia	8 (3)
Nausea	8 (3)
Anaemia	7 (3)
Chronic renal failure	7 (3)
Serious AEs†	3 (1)

Events are listed if they occurred in at least 3% of patients

Part B: Randomized withdrawal phase*

AEs, n (%)	Placebo (n=52)	Patiromer (n=55)
Any	26 (50)	26 (47)
Headache	4 (8)	2 (4)
Supraventricular extrasystoles	1 (2)	2 (4)
Constipation	0	2 (4)
Diarrhoea	0	2 (4)
Nausea	0	2 (4)
Serious AEs†	1 (2)	0

Events are listed if they occurred in at least 4% of patients in the patiromer group

During the initial treatment phase and through its follow-up period, the incidence of hypokalaemia (serum potassium level <3.5 mmol/L) was 3.0%; *Including safety follow-up period for that phase, which was 1–2 weeks after discontinuation of the study drug; †All SAEs are included; none were considered related to the study drug.
SAE, serious adverse events

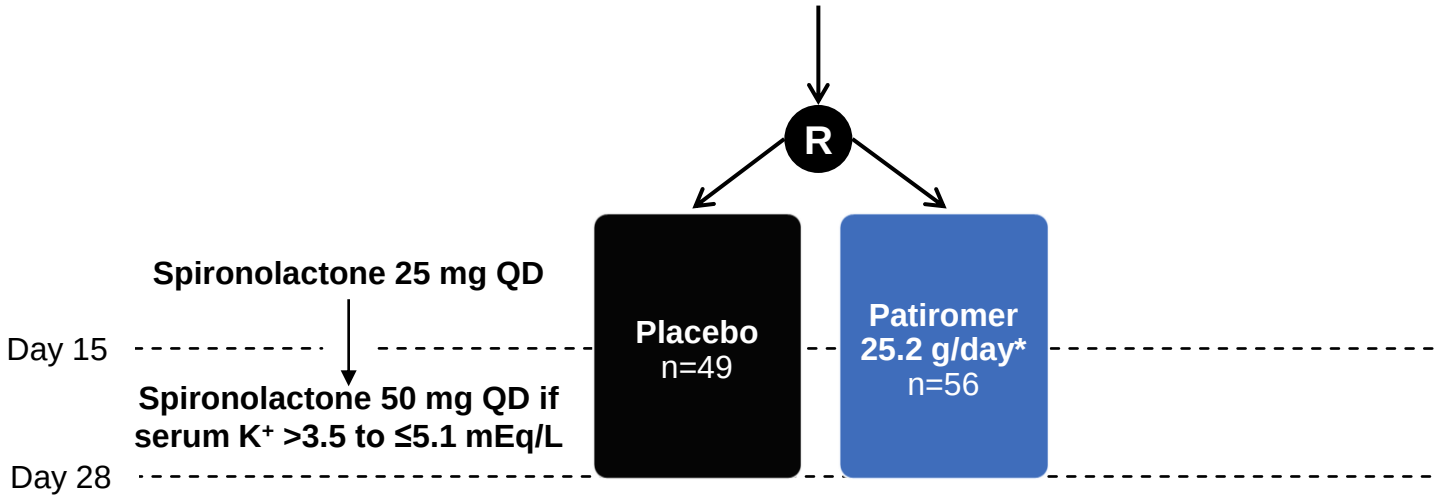
Weir MR *et al*. *N Engl J Med* 2015;372:211–21

PEARL-HF: Phase II, double-blind study in HF patients at high risk for HK and initiating spironolactone

Chronic HF, aged ≥18 years, clinically indicated to receive spironolactone and serum K^+ >4.3–5.1 mEq/L, and either of:

- **CKD (eGFR <60 mL/min) and on ≥1 RAASi (ACEi, ARB) or β-blocker**
- **Documented hyperkalaemia that led to discontinuation of RAASi or β-blocker within 6 months**

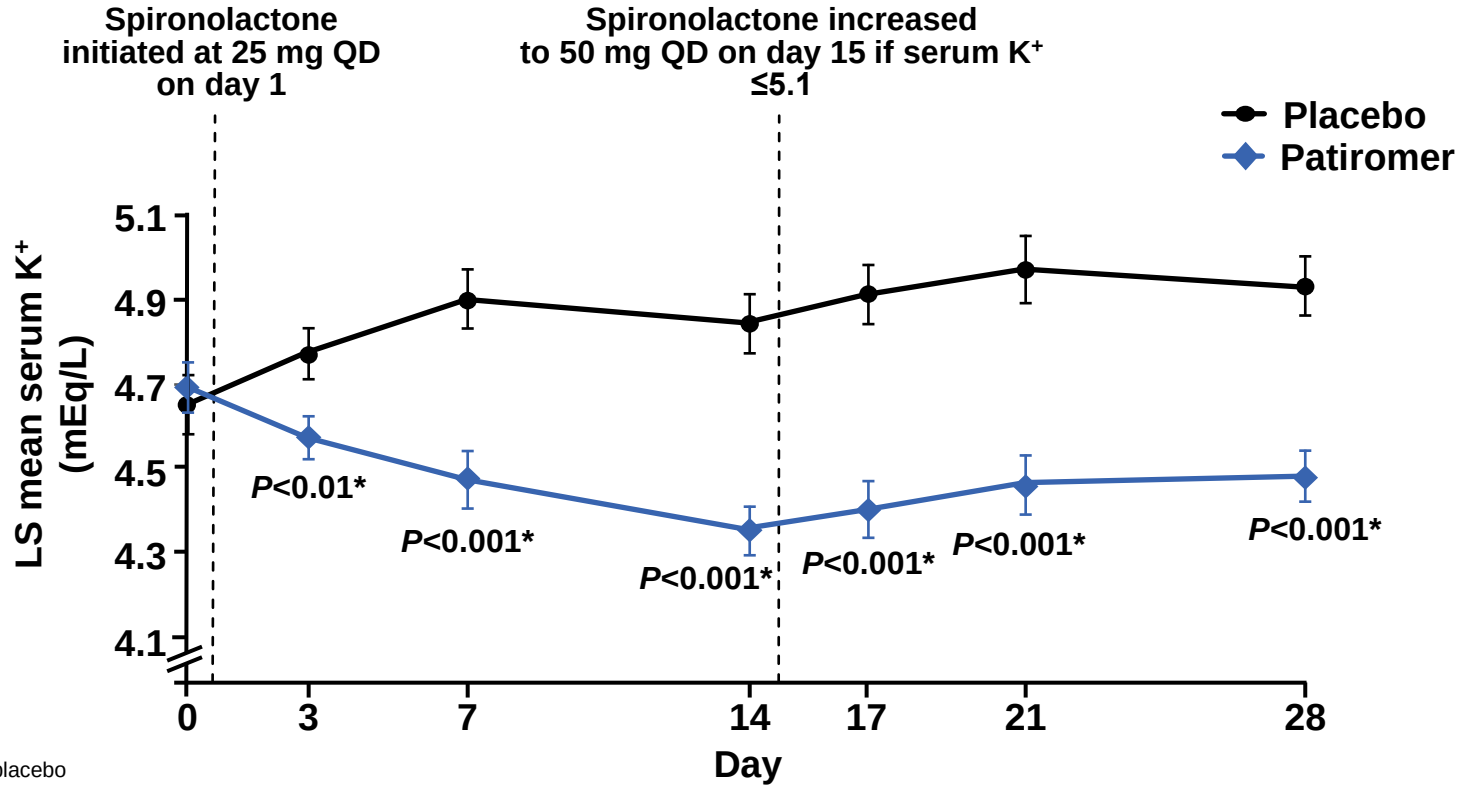
(n=120)



- *No patiromer dose titration

Pitt B *et al*. *Eur Heart J* 2011;32(7):820–8

PEARL-HF: Primary endpoint



*versus placebo
LS, least squares

Pitt B *et al*. *Eur Heart J* 2011;32(7):820–8

PEARL-HF: Up-titration of spironolactone

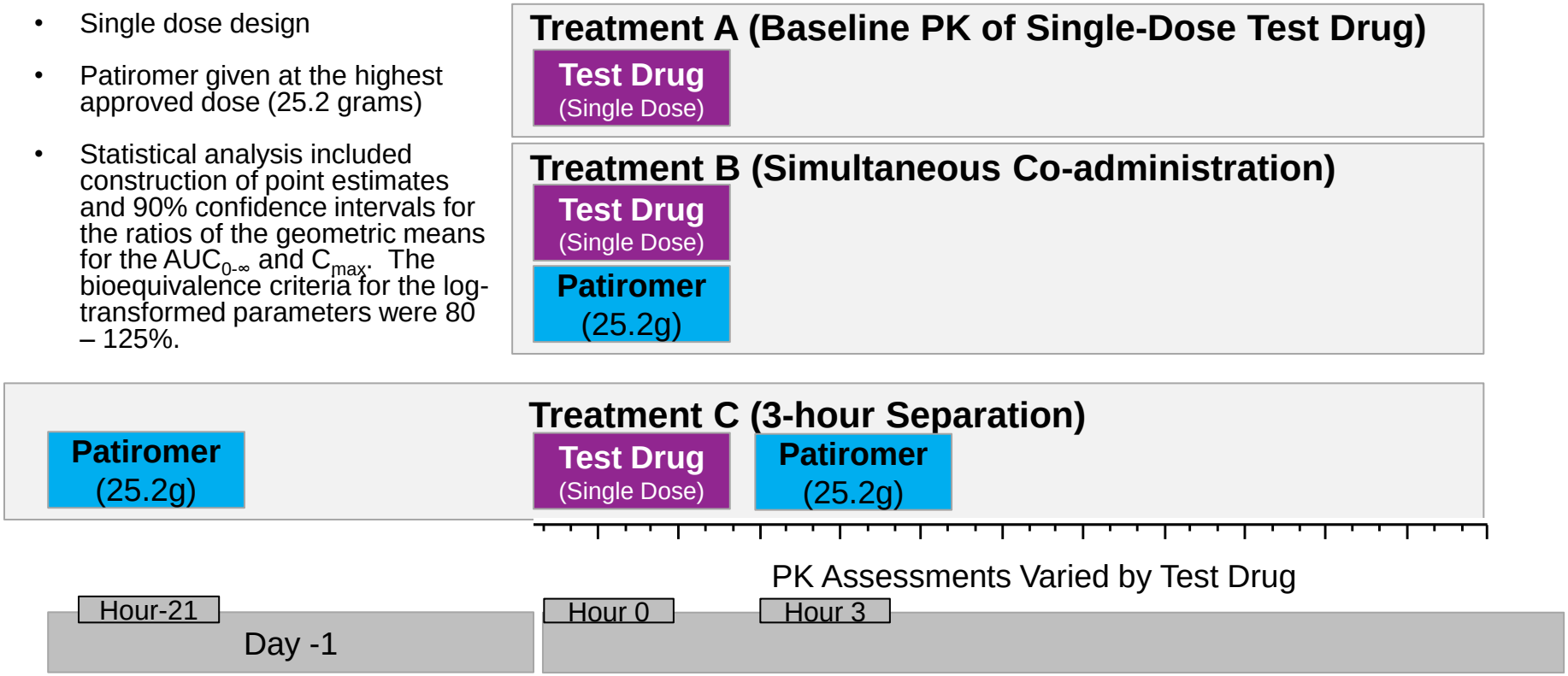
Patients able to titrate up spironolactone dose to 50 mg daily

	Placebo (n=49)	Patiromer (n=55)	*P*-value
Total, n (%)	**36 (74)**	**50 (91)**	**0.019**

Pitt B *et al*. *Eur Heart J* 2011;32(7):820–8

Drug Drug interaction study

- Single dose design
- Patiromer given at the highest approved dose (25.2 grams)
- Statistical analysis included construction of point estimates and 90% confidence intervals for the ratios of the geometric means for the $AUC_{0-\infty}$ and C_{max}. The bioequivalence criteria for the log-transformed parameters were 80 – 125%.

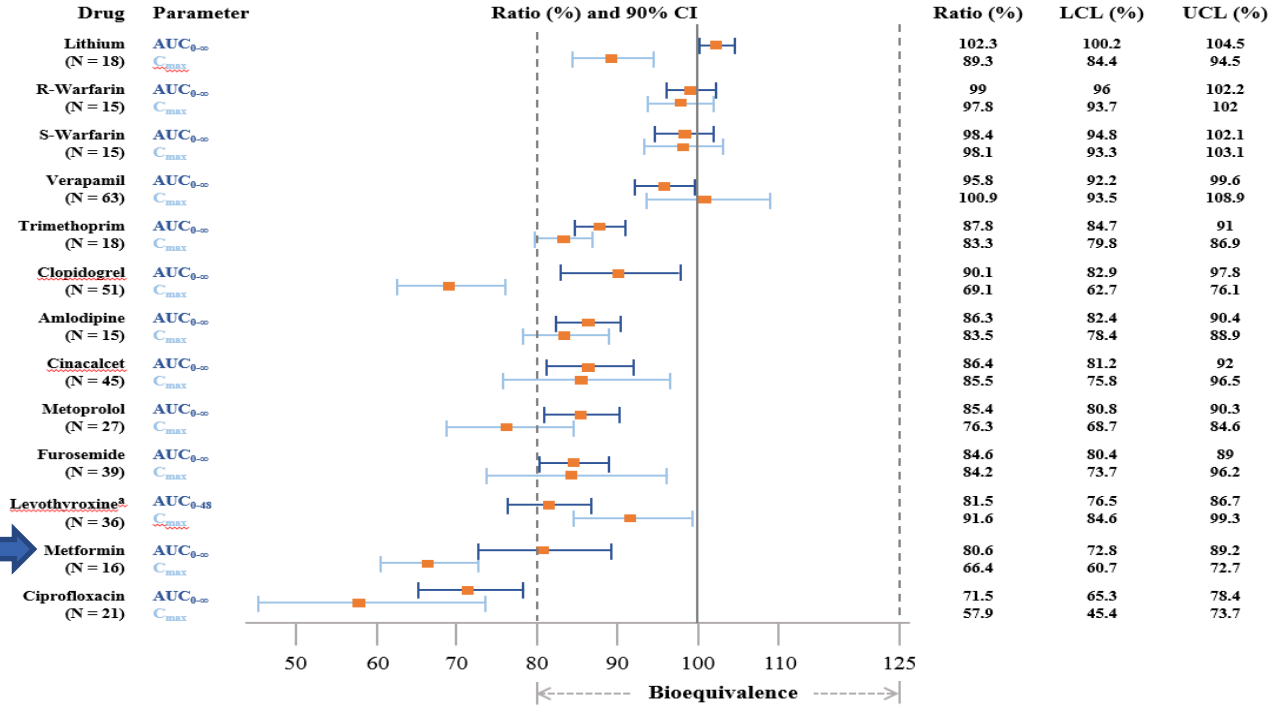


Lesko L., et al., Journal of Cardiovascular Pharmacology and Therapeutics 2017

Drug Drug interaction study - results

Geometric Mean Ratios ($AUC_{0-\infty}$, C_{max}): **Co-administered**

When concomitantly taking metformin with Veltassa®, the main effect is a reduction in the bioavailability of metformin. The reduction is of the same magnitude as when metformin is taken with food.



[a] As levothyroxine is recommended to be administered ½ hour to 1 hour before breakfast and patiromer is recommended to be administered with food, the two drugs were not administered at the same time and co-administration represents a 40 minute separation between levothyroxine and patiromer. Values adjusted for baseline thyroxine concentration; AUC for 48-hour sampling profile (AUC_{0-48}) shown because extrapolation to infinity is not valid for levothyroxine.

Abbreviations: $AUC_{0-\infty}$, area under the plasma concentration time curve from time 0 extrapolated to infinity; AUC_{0-48}, area under the plasma concentration time curve from time 0 to 48-hour sampling; CI, confidence interval; C_{max}, maximum observed plasma concentration; LCL, lower confidence interval limit; N, number of subjects planned for enrollment for each drug evaluated; UCL, upper confidence interval limit.

Lesko L., et al., Journal of Cardiovascular Pharmacology and Therapeutics 2017

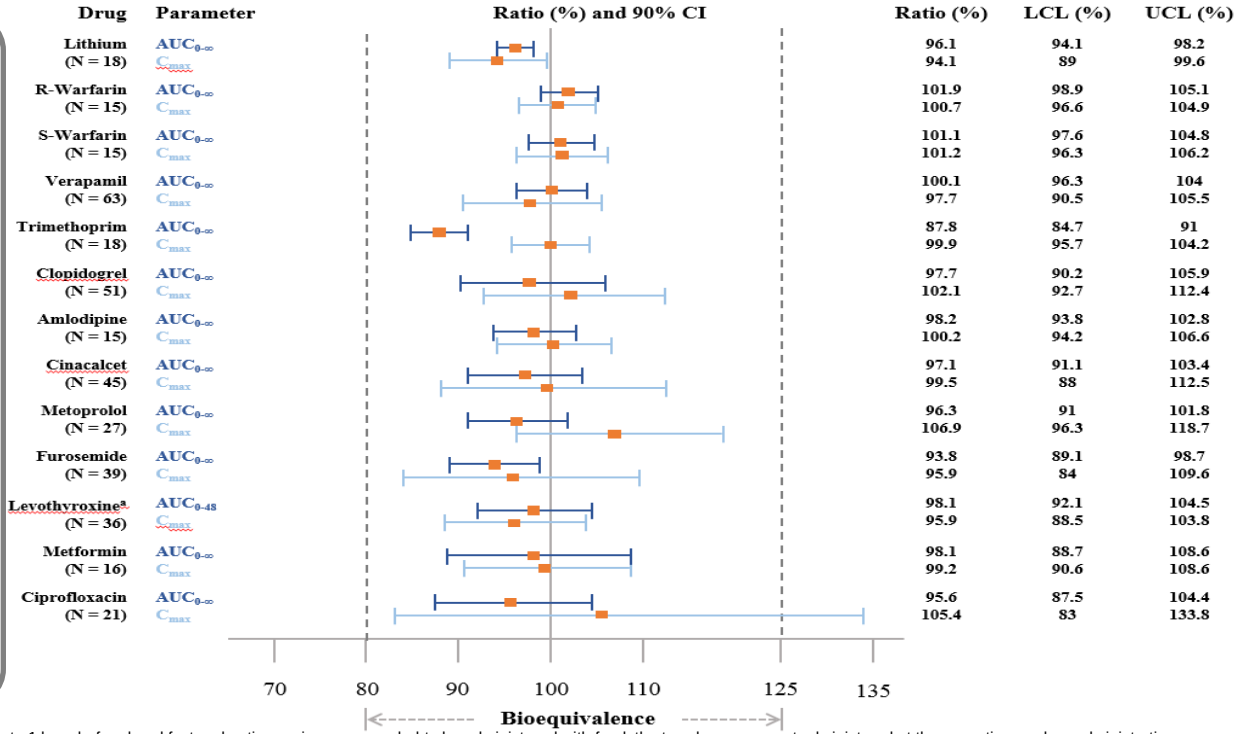
Drug Drug interaction study - results[1]

Geometric Mean Ratios ($AUC_{0-\infty}$, C_{max}): **3-Hour Separation**

Veltassa® EU Summary of Product Characteristics:

Patiromer has the potential to bind some oral co-administered medicinal products, which could decrease their gastrointestinal absorption.

***As precautionary measure**, and based on the data summarised below, **administration of patiromer should therefore be separated by at least 3 hours from other oral medicinal products**.[2]*



[a]As levothyroxine is recommended to be administered ½ hour to 1 hour before breakfast and patiromer is recommended to be administered with food, the two drugs were not administered at the same time and co-administration represents a 40 minute separation between levothyroxine and patiromer. Values adjusted for baseline thyroxine concentration; AUC for 48-hour sampling profile (AUC0-48) shown because extrapolation to infinity is not valid for levothyroxine. AUC for 48-hour sampling profile (AUC0-48) shown because extrapolation to infinity is not valid for levothyroxine.

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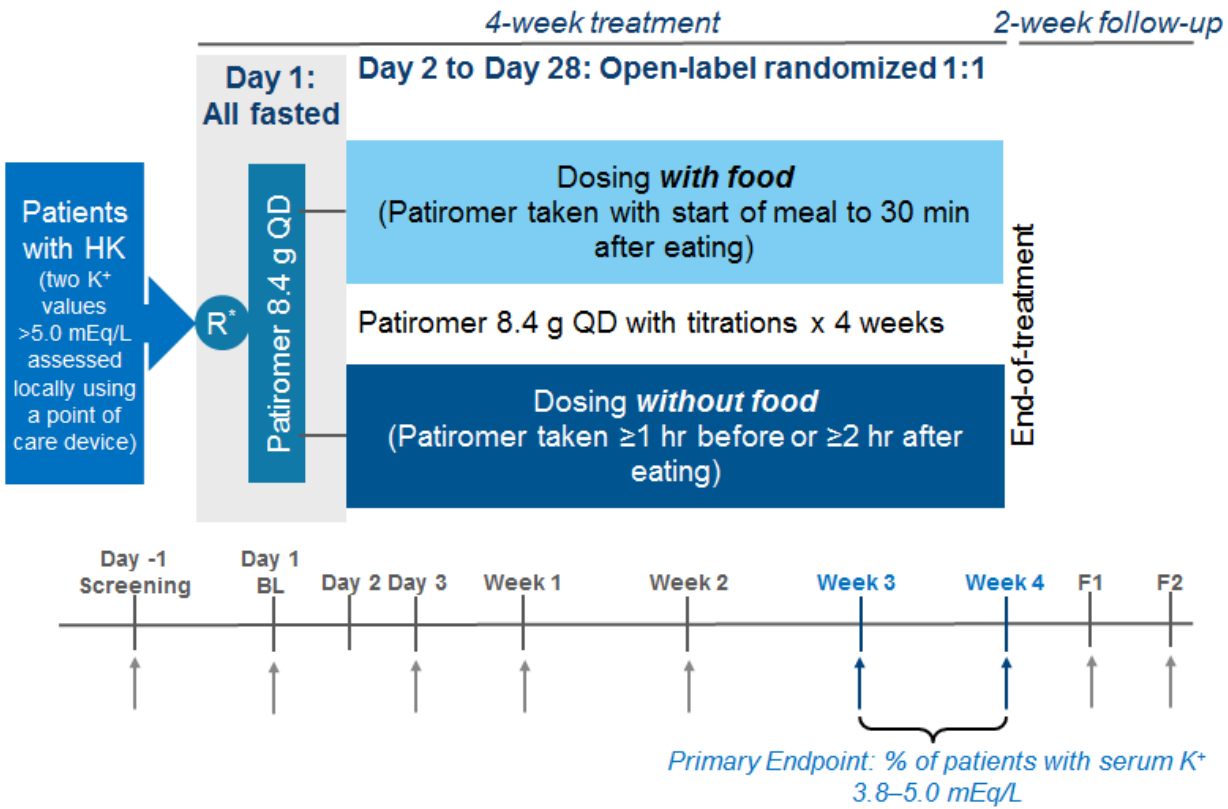
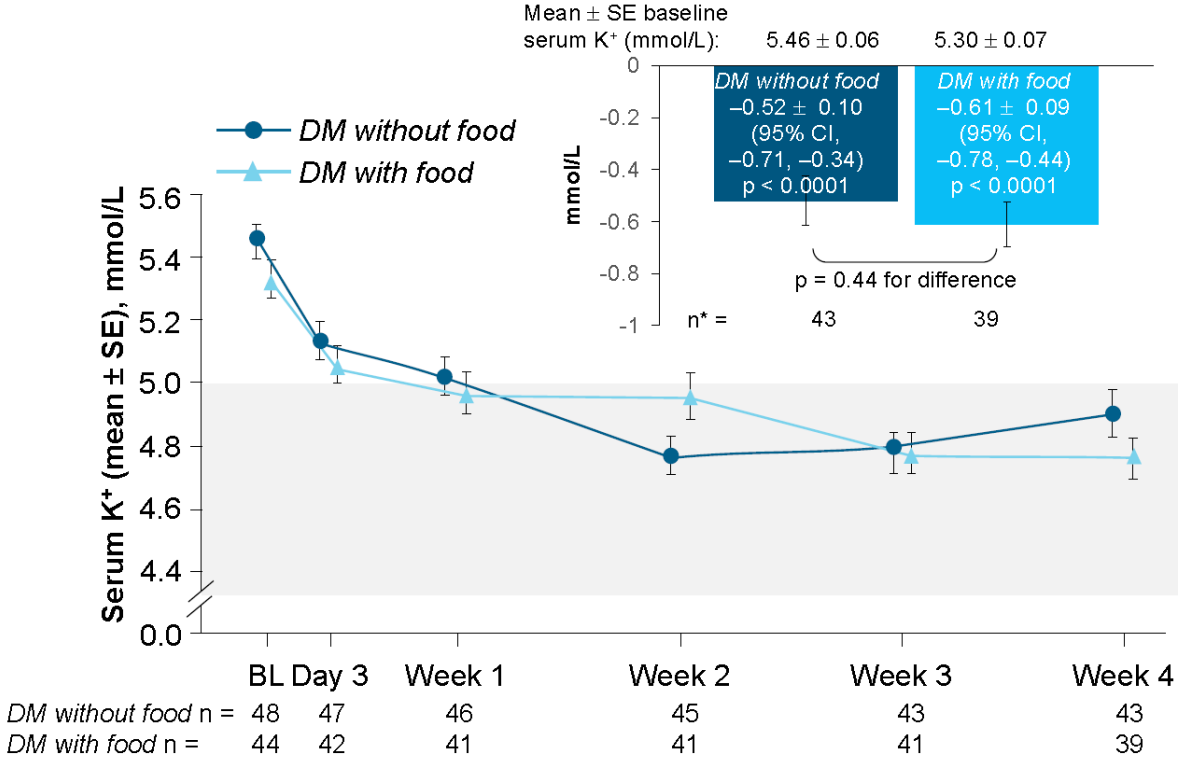
1. Lesko L., et al., Journal of Cardiovascular Pharmacology and Therapeutics 2017; 2. Veltassa® EU SmPC 2017

TOURMALINE – Study design



Rossignol P., et al. 53rd EASD Annual Meeting, 11–15 September 2017; Lisbon; Poster 1214

TOURMALINE – Serum potassium over time



*Patients who had both baseline and week 4 values were included in the analysis.

Rossignol P., et al. 53rd EASD Annual Meeting, 11–15 September 2017; Lisbon; Poster 1214

TOURMALINE – Safety

No. of patients (%)	Patient With DM Receiving Patiromer		DM Subgroup Overall (N = 93)
	Without Food (N = 48)	*With Food* (N = 45)	
With ≥1 AE	22 (45.8)	23 (51.1)	45 (48.4)
Most common* AEs			
Diarrhea	3 (6.3)	3 (6.7)	6 (6.5)
Blood creatine phosphokinase increased	1 (2.1)	2 (4.4)	3 (3.2)
Constipation	1 (2.1)	2 (4.4)	3 (3.2)
Headache	0	3 (6.7)	3 (3.2)
Urinary tract infection	1 (2.1)	2 (4.4)	3 (3.2)

No. of patients (%)	Patient With DM Receiving Patiromer		DM Subgroup Overall (N = 93)
	Without Food (N = 48)	*With Food* (N = 45)	
With ≥1 treatment-related AE	5 (10.4)	6 (13.3)	11 (11.8)
Most common* treatment-related AE			
Diarrhea (none severe)	1 (2.1)	2 (4.4)	3 (3.2)
With ≥1 AE leading to study discontinuation	2 (4.2)	1 (2.2)	3 (3.2)
With ≥1 serious AE†	3 (6.3)	1 (2.2)	4 (4.3)
Death	1 (2.1)	0	1 (1.1)
Prespecified laboratory values of interest			
Serum K^+ <3.5 mmol/L	0	0	0
Serum Mg <1.4 mg/dL‡ (<0.58 mmol/L)	3 (6.3)	2 (4.5)	5 (5.4)

Rossignol P., et al. 53rd EASD Annual Meeting, 11 – 15 September 2017; Lisbon; Poster 1214

AMBER Protocol Review

A Randomized, Double-Blind, Placebo-controlled, Parallel Group Study of Patiromer for the Enablement of Spironolactone Use for Blood Pressure Control in Patients with Resistant Hypertension and Chronic Kidney Disease: Evaluation of Safety and Efficacy (AMBER)

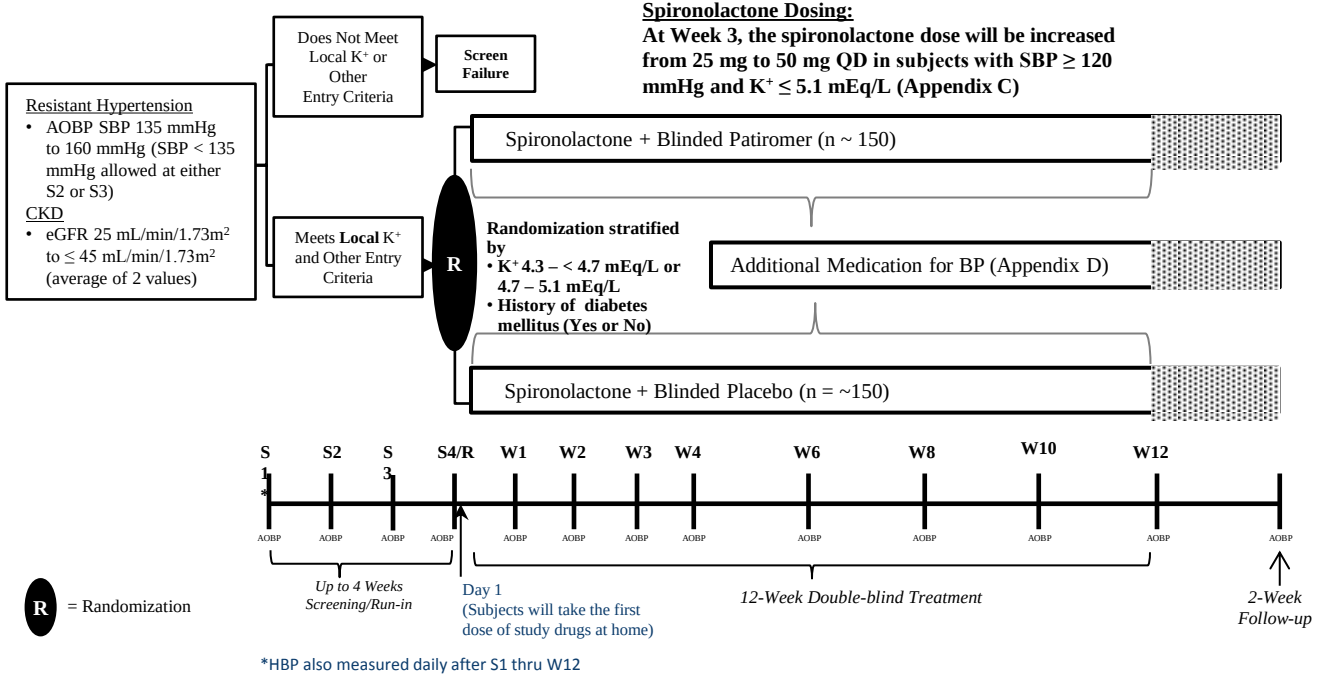
Rajiv Agarwal, Patrick Rossignol, Bill White, Brian Williams, D. Garza

07 Nov 2016

Study Objectives

To determine

- if patiromer treatment of subjects with CKD receiving spironolactone for the treatment of resistant hypertension will result in more persistent use of spironolactone through prevention of hyperkalemia and thereby,
- lead to improved blood pressure control compared with treatment with spironolactone alone (placebo)


Resistant Hypertension
• AOBP SBP 135 mmHg to 160 mmHg (SBP < 135 mmHg allowed at either S2 or S3)
CKD
• eGFR 25 mL/min/1.73m² to ≤ 45 mL/min/1.73m² (average of 2 values)
Does Not Meet Local K⁺ or Other Entry Criteria
Screen Failure
Meets Local K⁺ and Other Entry Criteria
R
Randomization stratified by
• K⁺ 4.3 – < 4.7 mEq/L or 4.7 – 5.1 mEq/L
• History of diabetes mellitus (Yes or No)
Spironolactone + Blinded Patiromer (n ~ 150)
Additional Medication for BP (Appendix D)
Spironolactone + Blinded Placebo (n = ~150)
Spironolactone Dosing:
At Week 3, the spironolactone dose will be increased from 25 mg to 50 mg QD in subjects with SBP ≥ 120 mmHg and K⁺ ≤ 5.1 mEq/L (Appendix C)
S1*
S2
S3
S4/R
W1
W2
W3
W4
W6
W8
W10
W12
AOBP
Up to 4 Weeks Screening/Run-in
Day 1
(Subjects will take the first dose of study drugs at home)
12-Week Double-blind Treatment
2-Week Follow-up
R = Randomization
*HBP also measured daily after S1 thru W12

Patients on RAASi were the primary patient population included into phase II – III program

RAASi medications at baseline, n(%)	Study 201 (N=6)	Study 202 (N=56)	Study 204 (N=63)	Study 205 (N=304)	Study 301A (N=243)	Study 301B patiromer patients[1] (N=55)	Total[2] (N=672)
Any RAASi	3 (50%)	55 (98.2%)	63 (100%)	304 (100%)	243 (100%)	55 (100%)	668 (**99.4%**)
ACE only	2 (33.3%)	1 (1.8%)	0	160 (52.6%)	136 (56.0%)	30 (54.5%)	299 (44.5%)
ARB only	1 (16.7%)	0	0	88 (28.9%)	65 (26.7%)	15 (27.3%)	154 (22.9%)
MRA only	0	3 (5.4%)	1 (1.6%)	0	2 (0.8%)	0	6 (0.9%)
ACE + ARB	0	0	0	31 (10.2%)	20 (8.2%)	6 (10.9%)	51 (7.6%)
ACE + MRA	0	42 (75.0%)	44 (69.8%)	2 (0.7%)	13 (5.3%)	1 (1.8%)	101 (15%)
ARB + MRA	0	7 (12.5%)	17 (27.0%)	17 (5.6%)	6 (2.5%)	3 (5.5%)	47 (7%)
ACE + ARB + MRA	0	2 (3.6%)	1 (1.6%)	6 (2.0%)	1 (0.4%)	0	10 (1.5%)

COMORBIDITES: PROFIL DES PATIENTS INCLUS DANS LES ETUDES DE PHASE II ET III

	Essai 201[2] Hemodialysis subjects (N=6)	Essai 202 [3,4] PEARL-HF (N=55)	Essai 204[5] CKD with HF (N=63)	Essai 205[6] AMETHYST-DN (N=304)	Essai 301[7,8] OPAL-HK (N=243)
DT2 nb (%)	-	20 (37)	23 (37)	304 (100)	139 (57)
ICC nb (%)	-	55 (100)	63 (100)	106 (35)	102 (42)
HTA nb (%)	4 (67)	-	-	304 (100)	236 (97)
IRC: DFG ml/min/1.73 m² (moy ± DS)	< 15	78 ± 32	< 60	40.6 ± 50.7	35.4 ± 16.2
Kaliémie mEq/L	≥ 5.5	4.3 - 5.1	4.3 - 5.1	5.3	5.6

2. ClinicalTrials.gov. NCT02033317. Available at: https://clinicaltrials.gov/ct2/show/NCT02033317. ; https://www.karger.com/Article/Pdf/451067
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4. Buysse J, et al. *Future Cardiol.* 2012;8:17–28;
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DT2: Diabète Type 2; ICC: Insuffisance Cardiaque Chronique; HTA: Hypertension Artérielle; IRC: Insuffisance Rénale Chronique; DFG: Débit de Filtration Glomérulaire

Summary

- In clinical trials, the novel potassium binder patiromer demonstrated efficacy in the management of hyperkalaemia and is well tolerated compared with existing therapies
  - Patiromer has been studied in patients with HK, HF with or without CKD
- Patiromer offers a new option for the management of hyperkalaemia in cardio-renal patients who also require RAASi
- Patiromer has been available in the USA since December 2015 and has recently been approved in the EU in July 2017

4. INFORMATIONS CLINIQUES

4.1 Indications thérapeutiques

Veltassa est indiqué pour le traitement de l'hyperkaliémie chez l'adulte.

4.2 Posologie et mode d'administration

Posologie

La dose de départ recommandée est de 8,4 g de patiromer une fois par jour.

La dose de départ peut être ajustée à des intervalles d'une semaine ou plus, en fonction du taux de potassium sérique et de la plage cible souhaitée. La dose quotidienne peut être augmentée ou diminuée de 8,4 g, comme il convient pour atteindre la plage cible souhaitée, jusqu'à une dose maximale de 25,2 g par jour. Si le potassium sérique chute sous la plage souhaitée, la dose doit être réduite ou le traitement doit être arrêté.

En cas d'oubli d'une dose, celle-ci doit être prise dès que possible le même jour. La dose oubliée ne doit pas être prise avec la dose suivante.

L'administration de Veltassa doit être éloignée de 3 heures de la prise d'autres médicaments par voie orale (voir rubrique 4.5).

Le délai d'action de Veltassa est de 4 à 7 heures après l'administration. Veltassa ne doit pas remplacer le traitement d'urgence d'une hyperkaliémie mettant en jeu le pronostic vital.