**Supplemental Appendix**

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Agarwal R, Rossignol P, Budden J, et al. Patiromer and spironolactone in resistant hypertension and advanced CKD: analysis of the randomized AMBER trial.

Supplementary information is available on Kidney360's website.

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**Supplemental Appendix A. Adverse events indicative of worsening renal function.**

In the estimated glomerular filtration rate (eGFR) 25–<30 subgroup, rates of adverse events (AEs) indicative of worsening kidney function were consistent with those in the overall AMBER population. These included AEs of renal failure (1.5% in the eGFR 25–<30 subgroup and 1.7% in the overall population), renal impairment (9.1% in the eGFR 25–<30 subgroup and 7.8% overall), chronic kidney disease (CKD) (0 in the eGFR 25–<30 subgroup and 0.7% overall), and nephropathy (0 in the eGFR 25–<30 subgroup and 0.3% overall).

AEs indicative of worsening kidney function led to spironolactone dose reduction in 1 placebo-treated patient and 1 patiromer-treated patient in the eGFR 25–<30 subgroup and 5 placebo-treated patients and 9 patiromer-treated patients in the eGFR 30–45 subgroup. AEs indicative of worsening kidney function led to early discontinuation of spironolactone in none of placebo-treated patients and 1 patiromer-treated patient in the eGFR 25–<30 subgroup and 3 placebo-treated patients and 1 patiromer-treated patient in the eGFR 30–45 subgroup.

**Supplemental Appendix B. Serum calcium and magnesium levels above or below prespecified thresholds during the study.**

In patients in the eGFR 25–<30 subgroup, on-study serum calcium values >10.5 mg/dL (the upper limit of normal [ULN]) were observed in 2 patients in the placebo group (**Supplemental Table 3**). Both of these patients had screening or baseline serum calcium >10.5 mg/dL. In patients in the eGFR 30–45 subgroup, on-study serum calcium >10.5 mg/dL occurred in 3 patients in the placebo group (2 of 3 with screening/baseline serum calcium >10.5 mg/dL), and in 4 patients on patiromer (2 with baseline serum calcium >ULN); 1 patient in patiromer group also had an AE of hypercalcemia. This patient's serum calcium was 11.7 mg/dL at the time the AE was reported, and the AE resolved without a change in dosing of patiromer or spironolactone. Serum calcium returned to the normal range by the follow-up visit in all 4 patiromer-treated patients who had on-study calcium above the ULN.

Four patients (1 in the placebo group and 3 in the patiromer group) in the eGFR 30–45 subgroup had on study serum magnesium <1.4 mg/dL (none in the eGFR 25–<30 subgroup and none with serum magnesium <1.2 mg/dL; **Supplemental Table 3**). In two of these patients, serum magnesium was below the lower limit of normal (LLN; 1.8 mg/dL) at baseline. None of these patients had cardiac arrhythmias temporally associated with low magnesium levels, neuromuscular abnormalities, or serum potassium below the LLN (3.5 mEq/L). One patient in the patiromer group had serum magnesium in the normal range at baseline, and serum magnesium had returned to the normal range at the follow-up visit. Two patients on patiromer had AEs of hypomagnesemia. One had a laboratory serum magnesium value equal to 1.4 mg/dL at the time of the AE (1.7 mg/dL at baseline, 1.8 mg/dL at follow-up). The other patient had 3 separate AEs of hypomagnesemia, with lab values of 1.7 mg/dL at the time of each AE (2.0 mg/dL at baseline, 1.7 mg/dL at follow-up).

**Supplemental Table 1. Reasons for early discontinuation of study treatment by eGFR subgroup and treatment.**

| | eGFR 25–<30 Subgroup | | | eGFR 30–45 Subgroup | | |
|---|---|---|---|---|---|---|
| | SPIRO + PBO (n=34) | SPIRO + PAT (n=32) | Treatment Groups Combined (n=66) | SPIRO + PBO (n=114) | SPIRO + PAT (n=115) | Treatment Groups Combined (n=229) |
| Discontinued early from study treatment | 15 (44) | 5 (16) | 20 (30) | 35 (31) | 16 (14) | 51 (22) |
| Met 1 of 3 protocol-specified withdrawal criteria* for high serum $K^+$: | | | | | | |
| 1) Patiromer/placebo dose = max, confirmed* $K^+$ ≥5.5 and <6.0 | 4 (12) | 1 (3) | 5 (8) | 17 (15) | 2 (2) | 19 (8) |
| 2) Patiromer/placebo dose increased by 8.4 g/day, confirmed† $K^+$ ≥5.5 and <6.0 | 3 (9) | 0 | 3 (5) | 4 (4) | 6 (5) | 10 (4) |
| 3) Confirmed* $K^+$ ≥6.0 | 2 (6) | 1 (3) | 3 (5) | 4 (4) | 0 | 4 (2) |
| Had protocol-defined symptomatic hypotension‡ | 1 (3) | 2 (6) | 3 (5) | 1 (1) | 2 (2) | 3 (1) |
| Had protocol-defined decline in eGFR§ | 1 (3) | 1 (3) | 2 (3) | 3 (3) | 2 (2) | 5 (2) |
| Other | 5 (15) | 0 | 5 (8) | 6 (5) | 6 (5) | 12 (5) |
| Adverse event | 1 (3) | 0 | 1 (2) | 4 (4) | 3 (3) | 7 (3) |
| Patient withdrawal | 3 (9) | 0 | 3 (5) | 2 (2) | 1 (1) | 3 (1) |
| Low serum $K^+$ | 1 (3) | 0 | 1 (2) | 0 | 1 (1) | 1 (0.4) |
| Investigator decision | 0 | 0 | 0 | 0 | 1 (1) | 1 (0.4) |

Data are n (%). Note: patients could have more than one reason for discontinuing early from study treatment.
AOBP, automated office blood pressure; eGFR, estimated glomerular filtration rate; $K^+$, potassium; PAT, patiromer; PBO, placebo; SPIRO, spironolactone.
*Repeat $K^+$ measurement (taken within 1 day) that confirms the initial measurement.
†Repeat $K^+$ measurement (taken within 3 days after the 8.4 g/day dose increase) that confirms the initial measurement.
‡Systolic AOBP <100 mmHg, or symptoms of hypotension and systolic AOBP <120 mmHg.
§eGFR decrease of 30–50% or eGFR decrease of >50% from baseline that did not return to ≤30% of baseline within 4 weeks.

**Supplemental Table 2. Cumulative spironolactone dose over 12 weeks by eGFR subgroup and treatment.**

| | eGFR 25–<30 Subgroup | | eGFR 30–45 Subgroup | |
|---|---|---|---|---|
| | Spironolactone + Placebo (n=34) | Spironolactone + Patiromer (n=32) | Spironolactone + Placebo (n=114) | Spironolactone + Patiromer (n=115) |
| Cumulative dose of spironolactone, mean (SE) mg* | 2419.1 (231.0) | 3071.1 (146.1) | 2628.9 (103.8) | 2906.5 (94.1) |
| Difference between treatment groups (patiromer group minus placebo group), LS mean (SE) mg | 732.4 (274.3) | | 273.8 (139.7) | |

eGFR, estimated glomerular filtration rate; LS, least squares; SE, standard error.
*Cumulative dose of spironolactone = sum of actual doses taken.

**Supplemental Table 3. Prespecified laboratory values of interest by eGFR subgroup and treatment.**

| | eGFR 25–<30 Subgroup | | eGFR 30–45 Subgroup | |
|---|---|---|---|---|
| | Spironolactone + Placebo (n=34) | Spironolactone + Patiromer (n=32) | Spironolactone + Placebo (n=114) | Spironolactone + Patiromer (n=115) |
| Serum $K^+$ <3.8 mEq/L | | | | |
| At baseline | 0 | 0 | 1 | 0 |
| At any post-baseline through week 12 Visit | 1 | 2 | 3 | 4 |
| Serum $K^+$ <3.5 mEq/L | | | | |
| At baseline | 0 | 0 | 0 | 0 |
| At any post-baseline through week 12 Visit | 0 | 0 | 0 | 1 |
| Serum magnesium in the following range at baseline: | | | | |
| <1.4 mg/dL | 0 | 0 | 0 | 1 |
| <1.2 mg/dL | 0 | 0 | 0 | 0 |
| Serum magnesium in the following range at any post-baseline through week 12 Visit: | | | | |
| <1.4 mg/dL | 0 | 0 | 1 | 3 |
| <1.2 mg/dL | 0 | 0 | 0 | 0 |
| Serum magnesium in the following range at any time while on study medication: | | | | |
| <1.4 mg/dL | 0 | 0 | 1* | 3* |
| <1.2 mg/dL | 0 | 0 | 0* | 0* |
| Serum calcium <8.5 mg/dL: | | | | |
| At baseline | 3 | 5 | 2 | 2 |
| At any post-baseline through week 12 Visit | 8 | 6 | 13 | 14 |
| While on study medication | 7 | 6 | 13* | 12* |
| Serum calcium >10.5 mg/dL: | | | | |
| At baseline | 3 | 0 | 0 | 2 |
| At any post-baseline through week 12 Visit | 2 | 0 | 3 | 4 |
| While on study medication | 2 | 0 | 3* | 4* |

eGFR, estimated glomerular filtration rate; $K^+$ potassium.
*n=113 for PBO and n=114 for PAT (some patients were missing post-baseline data).

**Supplemental Table 4. eGFR and urine albumin/creatinine ratio change from baseline at week 12.**

| | eGFR 25–<30 Subgroup | | eGFR 30–45 Subgroup | |
|---|---|---|---|---|
| | Spironolactone + Placebo (n=34) | Spironolactone + Patiromer (n=32) | Spironolactone + Placebo (n=114) | Spironolactone + Patiromer (n=115) |
| eGFR change from baseline at week 12, mean (SE) mL/min/1.73m$^2$ | 1.3 (1.2) | 1.1 (1.1) | –3.1 (0.7) | –2.1 (0.7) |
| Urine albumin/creatinine ratio change from baseline at week 12, mean (SE) mg/g | –165 (70) | –34 (73) | –14 (42) | –26 (30) |

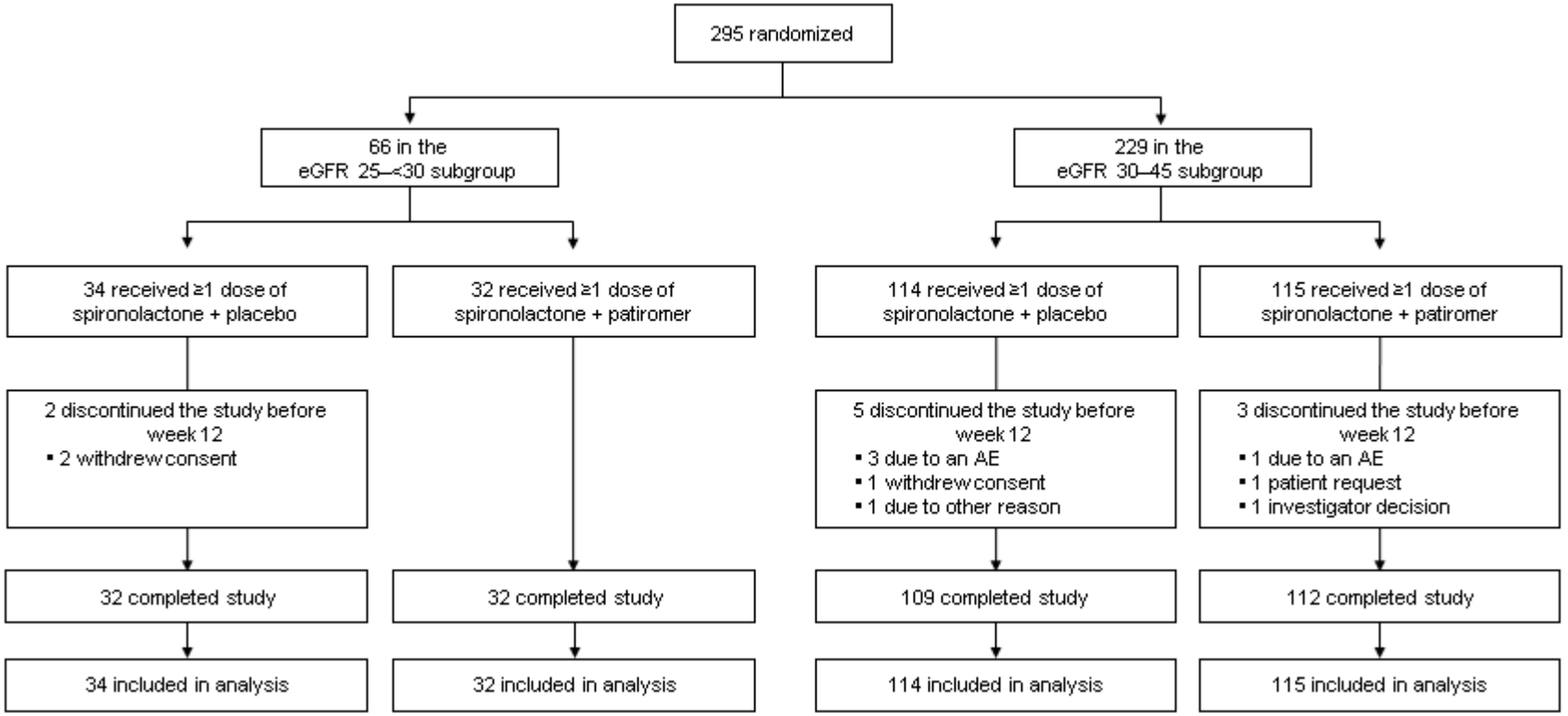
eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate; SE, standard error.

**Supplemental Table 5. Serum calcium and magnesium levels results over time and change from baseline.**

| | eGFR 25–<30 Subgroup | | eGFR 30–45 Subgroup | |
|---|---|---|---|---|
| | Spironolactone + Placebo (n=34) | Spironolactone + Patiromer (n=32) | Spironolactone + Placebo (n=114) | Spironolactone + Patiromer (n=115) |
| Magnesium, mean (SE) mg/dL | | | | |
| Baseline | 2.24 (0.05) | 2.10 (0.05) | 2.06 (0.02) | 2.11 (0.03) |
| Week 1 | 2.28 (0.05) | 2.08 (0.05) | 2.07 (0.02) | 2.06 (0.03) |
| Week 2 | 2.25 (0.04) | 2.09 (0.06) | 2.11 (0.02) | 2.04 (0.03) |
| Week 3 | 2.18 (0.04) | 2.13 (0.05) | 2.12 (0.03) | 2.11 (0.03) |
| Week 4 | 2.17 (0.04) | 2.04 (0.05) | 2.08 (0.02) | 2.05 (0.03) |
| Week 6 | 2.18 (0.04) | 2.06 (0.05) | 2.10 (0.02) | 2.05 (0.03) |
| Week 8 | 2.18 (0.04) | 2.11 (0.05) | 2.08 (0.03) | 2.05 (0.03) |
| Week 10 | 2.22 (0.04) | 2.14 (0.06) | 2.08 (0.03) | 2.06 (0.03) |
| Week 12 | 2.21 (0.04) | 2.09 (0.05) | 2.08 (0.02) | 2.02 (0.03) |
| Change from baseline to week 12 | –0.06 (0.04) | –0.01 (0.04) | 0.01 (0.02) | –0.08 (0.02) |
| Follow-up | 2.24 (0.05) | 2.20 (0.06) | 2.13 (0.02) | 2.14 (0.03) |
| Change from baseline to follow-up | –0.03 (0.04) | 0.13 (0.04) | 0.06 (0.02) | 0.03 (0.02) |
| Calcium, mean (SE) mg/dL | | | | |
| Baseline | 9.34 (0.15) | 9.03 (0.14) | 9.26 (0.05) | 9.33 (0.04) |
| Week 1 | 9.35 (0.16) | 9.10 (0.13) | 9.33 (0.05) | 9.36 (0.04) |
| Week 2 | 9.49 (0.15) | 9.23 (0.10) | 9.32 (0.05) | 9.41 (0.04) |
| Week 3 | 9.31 (0.16) | 9.18 (0.10) | 9.28 (0.05) | 9.31 (0.05) |
| Week 4 | 9.34 (0.15) | 9.12 (0.11) | 9.29 (0.05) | 9.34 (0.04) |
| Week 6 | 9.26 (0.12) | 9.16 (0.11) | 9.31 (0.05) | 9.35 (0.04) |
| Week 8 | 9.20 (0.15) | 9.11 (0.10) | 9.23 (0.05) | 9.29 (0.04) |
| Week 10 | 9.23 (0.14) | 9.04 (0.10) | 9.28 (0.05) | 9.30 (0.04) |
| Week 12 | 9.14 (0.17) | 9.08 (0.10) | 9.24 (0.05) | 9.26 (0.04) |
| Change from baseline to week 12 | –0.16 (0.09) | 0.06 (0.07) | –0.01 (0.04) | –0.07 (0.04) |
| Follow-up | 9.11 (0.16) | 9.04 (0.11) | 9.18 (0.06) | 9.23 (0.04) |
| Change from baseline to follow-up | –0.17 (0.08) | 0.04 (0.08) | –0.07 (0.04) | –0.08 (0.04) |

eGFR, estimated glomerular filtration rate; SE, standard error.

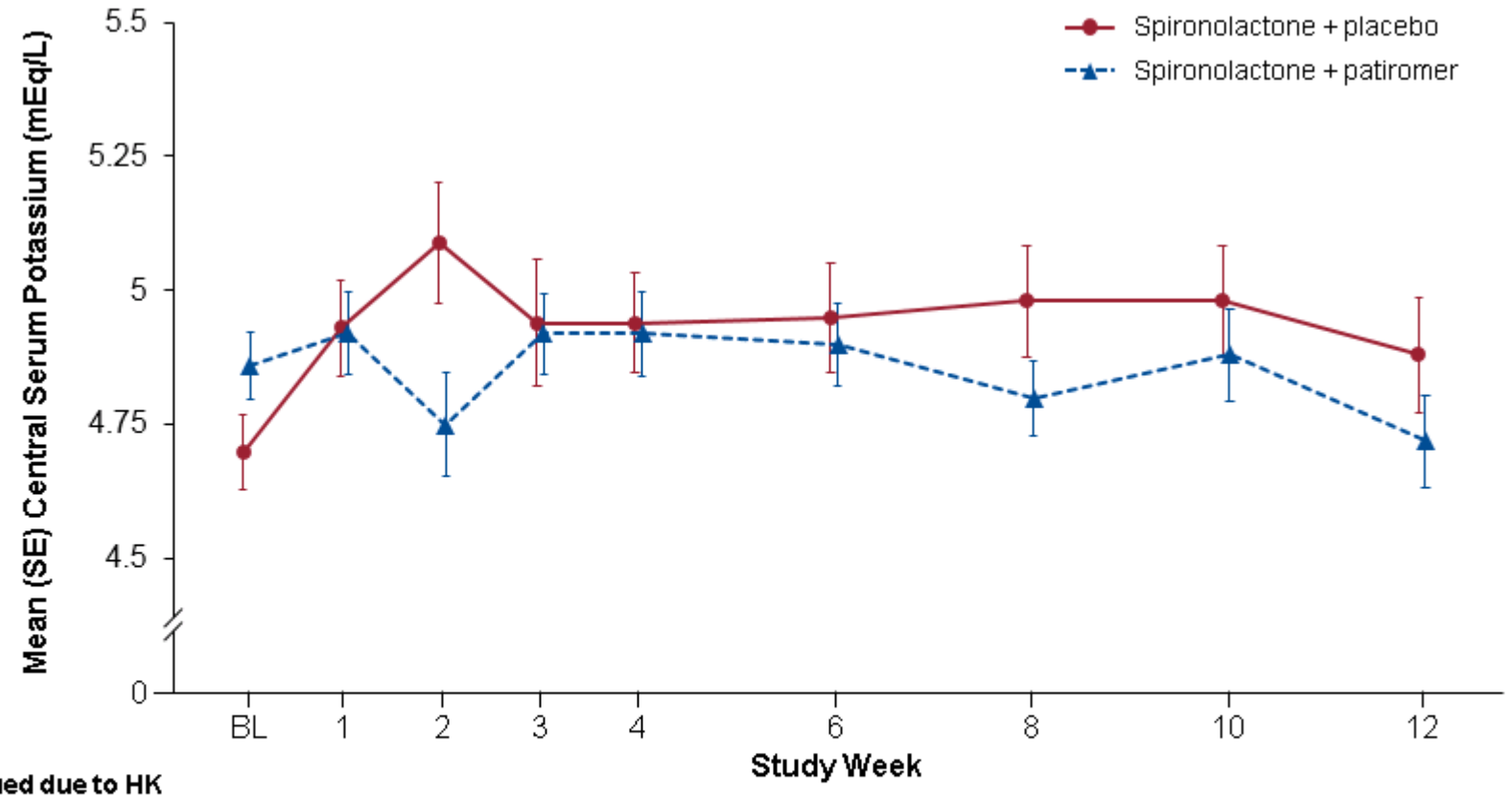
**Supplemental Figure 1. Patient disposition by eGFR subgroups.**




AE, adverse event; eGFR, estimated glomerular filtration rate.

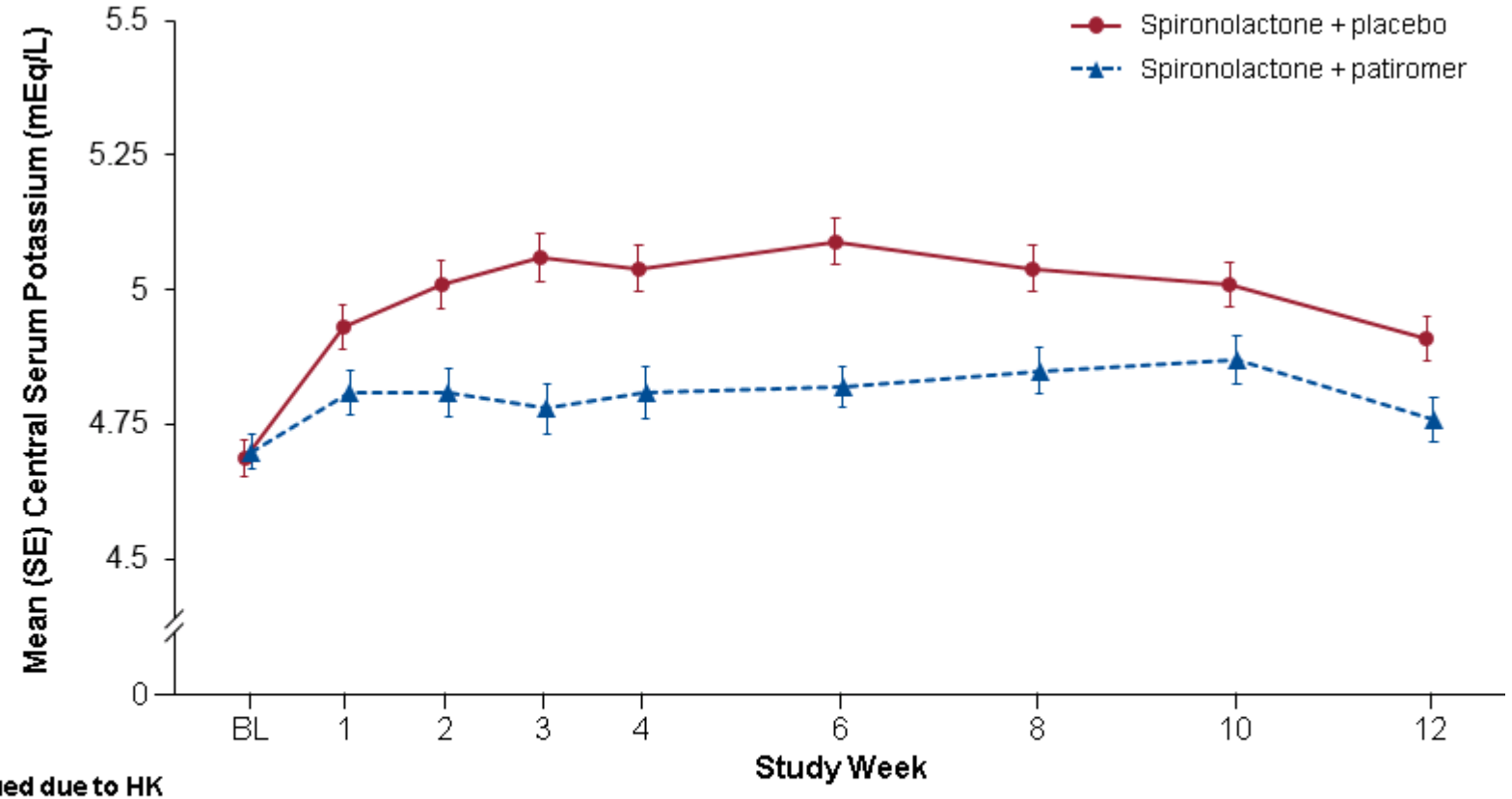
**Supplemental Figure 2. Mean (SE) central laboratory serum potassium during active treatment in the A) eGFR 25–<30 subgroup, and B) eGFR 30–45 subgroup.**

A)




| | BL | 1 | 2 | 3 | 4 | 6 | 8 | 10 | 12 |
|---|---|---|---|---|---|---|---|---|---|
| **Discontinued due to HK** | | | | | | | | | |
| Spironolactone + placebo | 0 | 0 | 2 | 1 | 1 | 0 | 2 | 2 | 1 |
| Spironolactone + patiromer | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0 |
| **Observed patients** | | | | | | | | | |
| Spironolactone + placebo | 34 | 34 | 34 | 32 | 32 | 32 | 32 | 31 | 32 |
| Spironolactone + patiromer | 32 | 32 | 32 | 32 | 32 | 32 | 32 | 32 | 32 |

B)




| | BL | 1 | 2 | 3 | 4 | 6 | 8 | 10 | 12 |
|---|---|---|---|---|---|---|---|---|---|
| **Discontinued due to HK** | | | | | | | | | |
| Spironolactone + placebo | 0 | 1 | 1 | 3 | 3 | 2 | 8 | 3 | 4 |
| Spironolactone + patiromer | 0 | 0 | 2 | 1 | 1 | 1 | 0 | 2 | 1 |
| **Observed patients** | | | | | | | | | |
| Spironolactone + placebo | 114 | 112 | 113 | 113 | 113 | 112 | 110 | 106 | 108 |
| Spironolactone + patiromer | 115 | 114 | 115 | 114 | 113 | 112 | 112 | 110 | 112 |

eGFR, estimated glomerular filtration rate; HK, hyperkalemia; SE, standard error.
Observed patients = Number of patients who have non-missing values at a study visit.
Discontinued patients = Number of patients who discontinued study treatment early for hyperkalemia at the study visit.