Patiromer to Enable Spironolactone in Patients With Resistant Hypertension and Chronic Kidney Disease (AMBER): Results in the Prespecified Subgroup With Diabetes

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INTRODUCTION

- PATHWAY-2 showed that spironolactone (SPIRO) was the most effective add-on drug for treatment of resistant hypertension (RHTN) and estimated glomerular filtration rate (eGFR) ≥45 mL/min/1.73m^2.[1]
- SPIRO is now recommended as an add-on drug for triple-antihypertensive therapy in patients with uncontrolled RHTN, including those with diabetes mellitus (DM).[2,3]
- However, SPIRO increases hyperkalemia (HK) risk, which can limit use in patients with advanced chronic kidney disease (CKD).[4]
- Patiromer (PAT) is a sodium-free, nonabsorbed potassium (K^+) binder approved in the United States and the European Union, among other countries, for the treatment of HK.[5-7]
- AMBER evaluated PAT to enable more persistent SPIRO use in patients with RHTN and an eGFR ≤45 mL/min/1.73m^2.[8]
  - Results showed 66% of placebo (PBO)–treated patients and 86% of PAT-treated patients remained on SPIRO at week 12 (20% between-group absolute difference; *P* <0.0001).

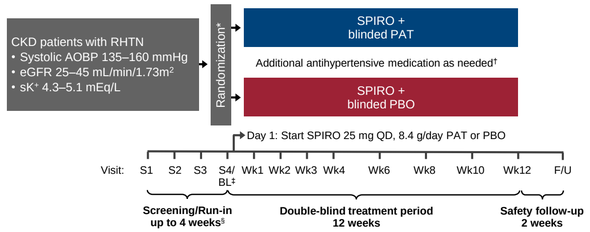
OBJECTIVE

- This analysis of the AMBER trial assessed the efficacy and safety of PAT to enable more persistent SPIRO use in prespecified subgroups with type 1 or 2 DM (DM^+) and without DM (DM^-).

METHODS

- AMBER was a randomized, double-blind, PBO-controlled, parallel group 12-week study of PAT and SPIRO vs PBO and SPIRO in patients with uncontrolled RHTN and CKD (**Figure 1**).
  - Patients were required to have serum K^+ (sK^+) between 4.3 and 5.1 mEq/L at screening.
  - RHTN was defined as unattended systolic automated office blood pressure (AOBP) of 135–160 mmHg during screening, despite taking 3 or more antihypertensive drugs (including a diuretic).
  - Patients had an eGFR of 25–45 mL/min/1.73m^2.
- All patients initiated SPIRO 25 mg once daily (QD) on day 1. Beginning at week 3, the SPIRO dose was increased to 50 mg QD for patients with systolic AOBP ≥120 mmHg and sK^+ ≤5.1 mEq/L.
- PAT/PBO was initiated at 8.4 g/day and adjusted in 8.4-g/day increments at intervals of ≥1 week, upward in patients with sK^+ >5.1 mEq/L and downward in patients with sK^+ <4.0 mEq/L.
- The between-group difference in patients remaining on SPIRO at week 12 was the primary endpoint, and the between-group difference in the change in systolic AOBP at week 12 was the secondary endpoint.

Figure 1. Study Design



*Stratified by local K^+ (4.3–<4.7 vs 4.7–5.1 mEq/L) and history of diabetes. †To maintain AOBP ≤200 mmHg. ‡For patients who meet all inclusion criteria, this visit becomes the randomization/baseline visit (day 0). §To ensure eligibility criteria, stable medication, and competent use of HBP monitor.

BL, baseline; F/U, follow-up; HBP, home blood pressure; S, screening; Wk, week.

RESULTS

- Baseline demographics and concomitant medications are shown in **Table 1**.
- Of 295 patients randomized, 49.2% had DM; 1.4% of these had type 1 DM (one patient in each treatment group).
- In the DM^+ subgroup, 47 (65%) patients randomized to PBO and 61 (84%) patients randomized to PAT completed the study (51 [67%] and 65 [88%] patients in the DM^- subgroup, respectively).

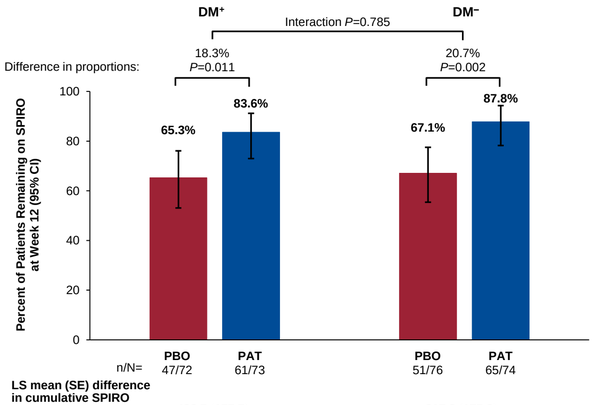
Table 1. Baseline Demographics and Clinical Characteristics by DM Subgroup

	DM^+		DM^-	
Parameter	SPIRO+PBO (n=72)	SPIRO+PAT (n=73)	SPIRO+PBO (n=76)	SPIRO+PAT (n=74)
Age at informed consent, mean (SD) years	69.5 (9.3)	66.5 (11.4)	67.6 (12.7)	69.1 (13.0)
Male, n (%)	33 (45.8)	45 (61.6)	44 (57.9)	31 (41.9)
BMI, mean (SD), kg/m^2	29.7 (5.0)	30.5 (4.2)	29.6 (4.5)	28.1 (5.1)
History of heart failure, n (%)	33 (45.8)	24 (32.9)	36 (47.4)	39 (52.7)
Systolic BP, mean (SD) mmHg	145.5 (6.4)	144.5 (6.9)	144.3 (7.6)	142.0 (5.9)
Central laboratory sK^+, mean (SD) mEq/L	4.75 (0.33)	4.77 (0.35)	4.64 (0.41)	4.70 (0.37)
Central laboratory eGFR, mean (SD) mL/min/1.73m^2	37.2 (7.1)	35.3 (7.1)	35.0 (7.9)	35.5 (7.5)
Central laboratory serum glucose, mean (SD) mg/dL	145.4 (51.64)	140.3 (52.56)	104.0 (24.93)	98.6 (16.13)
Urine albumin/creatinine ratio, mean (SD)	536.6 (908.7)	685.0 (1054.0)	258.4 (464.0)	182.8 (371.7)
Receiving insulins and insulin analogs, n (%)	18 (25.0)	26 (35.6)	0	0
Number of antihypertensive medications, mean (SD)*	3.7 (0.8)	3.8 (1.0)	3.5 (0.6)	3.7 (0.7)
Baseline concomitant medications				
Insulins and insulin analogues, n (%)	18 (25.0)	26 (35.6)	0	0
Noninsulin DM medications, n (%)	54 (75.0)	48 (65.8)	1 (1.3)	1 (1.4)
RAAS inhibitors, n (%)	72 (100)	73 (100)	75 (98.7)	74 (100)
Diuretics, n (%)	72 (100)	73 (100)	76 (100)	74 (100)
Beta-blockers, n (%)	53 (73.6)	44 (60.3)	44 (57.9)	57 (77.0)
Calcium channel blockers, n (%)	50 (69.4)	56 (76.7)	56 (73.7)	51 (68.9)

*Additions to antihypertensive medications before week 12 occurred in 4 PBO patients and 0 PAT patients. No additions in antihypertensive medications were reported to be due to new edematous states.

BMI, body mass index; BP, blood pressure; RAAS, renin-angiotensin-aldosterone system; SD; standard deviation.

Figure 2. Proportion of Patients Who Remained on SPIRO at Week 12 by DM Subgroup*

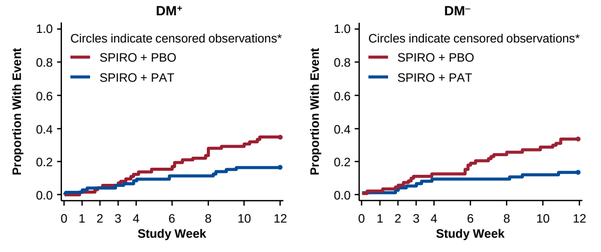


*Analysis used Cochrane-Mantel-Haenszel test stratified by baseline K^+ category (4.3–<4.7 vs 4.7–5.1 mEq/L) and presence of DM.

CI, confidence interval; LS, least squares; SE, standard error.

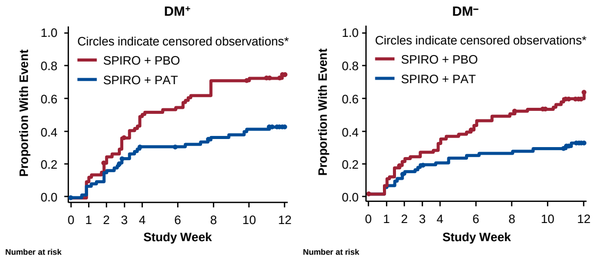
- In both DM subgroups, significantly more patients treated with PAT than PBO remained on SPIRO at week 12 and the cumulative SPIRO dose was higher with PAT than PBO (**Figure 2**). Time to early SPIRO discontinuation is shown in **Figure 3**.

Figure 3. Time to Early Discontinuation of SPIRO by DM Subgroup



*Patients who completed 12 weeks of study treatment and had not had any event are censored at week 12. Time to discontinuation was analyzed using Kaplan-Meier methods.

Figure 4. Time to First sK^+ Value ≥5.5 mEq/L During Treatment by DM Subgroup



*Patients who completed 12 weeks of study treatment and had not had any event are censored at week 12. Time to discontinuation was analyzed using Kaplan-Meier methods.

- Baseline mean (SD) sK^+ (mEq/L) was 4.76 (0.34) in the DM^+ and 4.67 (0.39) in the DM^- subgroups.
- Mean (SE) sK^+ change from baseline to week 12 was 0.06 (0.50) mEq/L for PAT and 0.10 (0.50) mEq/L for PBO in the DM^+ subgroup (–0.02 [0.44] mEq/L and 0.30 [0.51] mEq/L in the DM^- subgroup, respectively).
- sK^+ ≥5.5 mEq/L occurred in 30 (41.1%) PAT patients and 52 (72.2%) PBO patients in the DM^+ subgroup (22 [29.7%] and 43 [56.6%] in the DM^- subgroup, respectively). Time to first sK^+ ≥5.5 mEq/L is shown in **Figure 4**.
- AOBP decreased significantly from baseline in all DM^+ and DM^- treatment groups.
- LS mean (95% CI) difference in AOBP change between treatment groups was –0.75 (–4.7, 6.2) mmHg (*P*=0.788) for DM^+ and –2.55 (–6.6, 1.5) mmHg (*P*=0.219) for DM^- subgroups (*P*=0.239 for interaction between subgroups).

DISCLOSURES

RA reports personal fees from Abbvie, Akebia, Amgen, AstraZeneca, Bayer, Birdrock Bio, Boehringer Ingelheim, Celgene, Daiichi Sankyo, Eli Lilly, GlaxoSmithKline, Ironwood Pharmaceuticals, Johnson & Johnson, Merck, Novartis, Opko, Otsuka, Reata, Relypsa, Inc., a Vifor Pharma Group Company, Sandoz, Sanofi, Takeda; has served as associate editor of the *American Journal of Nephrology*, *Nephrology Dialysis and Transplantation*; and an author on *UpToDate*; and received research grants from the US Veterans Administration and the National Institutes of Health; **PR** reports consulting for G3P and Idorsia; honoraria from Ablative Solutions, AstraZeneca, Bayer, Boehringer-Ingelheim, Corvidia, CVRx, Fresenius, Grunenthal, Novartis, NovoNordisk, Relypsa, Inc., a Vifor Pharma Group Company, Sequana Medical, Servier, Stealth Peptides, and Vifor Fresenius Medical Care Renal Pharma; and travel grants from AstraZeneca, Bayer, CVRx, Novartis, and Vifor Fresenius Medical Care Renal Pharma; Cofounder: CardioRenal; **SA** and **AC** report employment by Relypsa, Inc., a Vifor Pharma Group Company, and stock in Vifor Pharma; **WBW** has nothing to disclose; **BW** reports honoraria for lectures on hypertension from Daichii Sankyo, Pfizer, Novartis, Servier, and Boehringer Ingelheim, and consulting for Novartis, Relypsa, Inc., a Vifor Pharma Group Company, and Vascular Dynamics Inc.

Table 2. Safety Summary by DM Subgroup

	DM^+		DM^-	
Parameter, n (%)	SPIRO+PBO (n=72)	SPIRO+PAT (n=73)	SPIRO+PBO (n=76)	SPIRO+PAT (n=74)
Adverse events (AEs)	44 (61.1)	44 (60.3)	35 (46.1)	38 (51.4)
Severe AEs	2 (2.8)	1 (1.4)	1 (1.3)	1 (1.4)
Serious AEs*	3 (4.2)	1 (1.4)	1 (1.3)	0
AE leading to study treatment discontinuation	8 (11.1)	5 (6.8)	13 (17.1)	5 (6.8)
Discontinuation for HK	4 (5.6)	1 (1.4)	7 (9.2)	1 (1.4)
AE leading to death	1 (1.4)	0	0	0
Most common AEs†				
HK or blood K^+ increased	7 (9.7)	8 (11.0)	7 (9.2)	1 (1.4)
Renal impairment	4 (5.6)	6 (8.2)	6 (7.9)	7 (9.5)
Headache	5 (6.9)	2 (2.7)	6 (7.9)	7 (9.5)
Diarrhea	7 (9.7)	4 (5.5)	1 (1.3)	5 (6.8)
Hypotension	3 (4.2)	4 (5.5)	3 (3.9)	5 (6.8)
GFR decreased	4 (5.6)	2 (2.7)	1 (1.3)	4 (5.4)
Nausea	6 (8.3)	3 (4.1)	1 (1.3)	0
Flatulence	2 (2.8)	4 (5.5)	2 (2.6)	2 (2.7)
Hyperglycemia or blood glucose increased	4 (5.6)	5 (6.8)	0	1 (1.4)
Influenza	0	3 (4.1)	4 (5.3)	3 (4.1)
Prespecified laboratory values of interest				
sK^+ <3.5 mEq/L	0	0	0	1 (1.4)
sMg^{2+} <1.4 mg/dL	1 (1.4)	2 (2.8)‡	0	1 (1.4)

*None were considered related to study drug in the opinion of the investigator. †Occurring in at least 5% of patients in any treatment group. ‡n=72.

sMg^{2+}, serum magnesium.

- AE rates were similar between groups. AEs occurring in ≥5% of patients in any treatment group are shown in **Table 2**.
- AEs were reported in 44 (60%) patients randomized to PAT and 44 (61%) randomized to PBO in the DM^+ subgroup (38 [51%] and 35 [46%] in the DM^- subgroup, respectively).
- Discontinuation due to AEs of HK occurred in 1.4% of the DM^+ PAT treatment group and 5.6% of the DM^+ PBO treatment group (1.4% and 9.2% in the DM^- subgroups, respectively).
- Patients with any post-baseline through week 12 sK^+ or sMg^{2+} measurements above or below prespecified thresholds are reported according to DM subgroup in **Table 2**.
  - One patient on PAT in the DM^- subgroup had sK^+ <3.5 mEq/L.
  - Four patients had at least one sMg^{2+} value <1.4 mg/dL (none <1.2 mg/dL). In 2 of these patients (both DM^+ PAT), sMg^{2+} 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 sMg^{2+} levels, neuromuscular abnormalities, or sK^+ below the LLN (3.5 mEq/L).

CONCLUSIONS

- In the AMBER study of patients with RHTN and advanced CKD (eGFR 25−45 mL/min/1.73m^2), the coadministration of PAT enabled more persistent use of SPIRO.[8]
- Results of the primary endpoint in the DM^+ and DM^- subgroups were consistent with those seen in the overall population with no significant difference between subgroups.
- AOBP decreased significantly in each DM subgroup with no difference between PAT or PBO treatment.
- The PAT safety profile is consistent with previous reports,[9,10] and the AMBER study adds PBO-controlled data to the safety database, including in patients with and without DM.

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