

**A Comparative Post Hoc Analysis of Finerenone and Spironolactone in Resistant Hypertension in Moderate-to-Advanced Chronic
Kidney Disease**

Supplemental Material

This supplement contains the following items:

Table S1. Follow-up Schedules, Dosing Regimen, and Serum Potassium–Monitoring Protocols of the FIDELIO-DKD, FIGARO-DKD, and AMBER Trials

Table S2. Confounding Factors in FIDELITY-TRH and the External Comparator (AMBER) Study

Table S1. Follow-up Schedules, Dosing Regimen, and Serum Potassium–Monitoring Protocols of the FIDELIO-DKD, FIGARO-DKD, and AMBER Trials

	FIDELITY-TRH ^{13,14,24}	AMBER ^{9,15}
Scheduled follow-up intervals	<ul style="list-style-type: none"> Scheduled visits took place at months 1, 4, and every 4 months thereafter, and, in addition, 1 month following any up-titration in dose of study medication 	<ul style="list-style-type: none"> Visits during the treatment period are weekly (weeks 1-4) and then biweekly (weeks 6-12)
[K ⁺] assessment	<ul style="list-style-type: none"> Measuring of serum [K⁺] occurred both locally and centrally; local serum [K⁺] levels were used to guide dosing and treatment interruption, as well as for safety purposes 	<ul style="list-style-type: none"> Local and central serum [K⁺] was measured
Dosing and monitoring	<ul style="list-style-type: none"> The starting dose of finerenone in participants with a screening eGFR of 25-<60 mL/min/1.73 m² and an eGFR ≥60 mL/min/1.73 m² was 10 mg and 20 mg, respectively^{13,14} 	<ul style="list-style-type: none"> Open-label spironolactone dosing started at 25 mg od and increased to 50 mg od at week 3 for patients with AOBP ≥120 mm Hg and serum [K⁺] ≤5.1 mmol/L

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	<ul style="list-style-type: none"> Investigators were encouraged to up-titrate the dose of the study medication to 20 mg after 1 month if serum [K⁺] remained ≤4.8 mmol/L and eGFR was stable^{13,14} If the measured serum [K⁺] was >4.8-≤5.5 mmol/L, investigators were instructed to maintain the study dose (10 mg od or 20 mg od), and if serum [K⁺] was >5.5 mmol/L, investigators were instructed to temporarily stop treatment, recheck the serum [K⁺] after 72 hours, and restart with a dose of 10 mg od when serum [K⁺] was ≤5.0 mmol/L^{13,14} Down-titration to finerenone 10 mg was permitted at any time in the event of any safety concerns K⁺ binder use was left up to the discretion of the treating physicians. 	<ul style="list-style-type: none"> Patients with AOBP <120 mm Hg and serum [K⁺] >5.1 mmol/L at week 3 continued on 25 mg od dosing until the first subsequent visit at which serum [K⁺] was ≤5.1 mmol/L, at which time the dose would be increased to 50 mg od.¹⁵ For decreases in eGFR of 30%-50%, the spironolactone dose should be decreased and eGFR monitored weekly¹⁵
Stopping criteria	<ul style="list-style-type: none"> Permanent discontinuation of the study drug was recommended if a patient on the 10 mg od dose experienced a recurrent hyperkalemia event soon after a previous event with interruption of study drug (provided the only explanation for the recurring hyperkalemia event was the study drug), or if, in the opinion of the investigator, continuation of treatment was harmful to the patient²⁴ 	<ul style="list-style-type: none"> Criteria for treatment withdrawal because of high serum [K⁺] included the following: [K⁺] ≥5.5 mmol/L and <6.0 mmol/L, on maximum dose of patiromer or placebo, and repeat [K⁺] within 1 day remained ≥5.5 mmol/L; [K⁺] ≥5.5 mmol/L and <6.0 mmol/L, not on maximum dose but after dose was increased by 2 packets, and repeat [K⁺] within 3 days remained ≥5.5 mmol/L; and [K⁺] ≥6.0 mmol/L and repeat [K⁺] within 1 day remained ≥6.0 mmol/L Patients who discontinued patiromer or placebo were required to discontinue spironolactone at the same time Spironolactone should be discontinued if eGFR does not return to within 30% of baseline within 4 weeks¹⁵ For eGFR decreases >50%, spironolactone should be discontinued and eGFR monitored weekly until it returns to within 15% of baseline¹⁵

	FIDELITY-TRH ^{13,14,24}	AMBER ^{9,15}
BP monitoring	<ul style="list-style-type: none"> • BP was measured at all scheduled visits, using an automated sphygmomanometer with an appropriate cuff size in the sitting position after 5 minutes of rest • The requirement was 3 consecutive BP readings, with at least a 1-minute interval between each reading and all 3 readings recorded within 20 minutes • If BP was considered uncontrolled during the study period, a non-potassium-sparing diuretic could be added 	<ul style="list-style-type: none"> • BP was measured at each visit, using an oscillometric monitoring device, which allowed a 5-minute rest period before initiating a sequence of triplicate measurements with a 1-minute interval between each measurement • No observer was present for these automated measurements • Patients were provided with a home BP monitor at the first use and were instructed to measure home BP in triplicate twice daily at the same time each day after 5 minutes of seated rest; they brought the monitor to each visit and measured BP after the AOBP

FIDELITY-TRH population refers to patients with TRH and moderate-to-advanced CKD.

Abbreviations: AMBER, Spironolactone With Patiromer in the Treatment of Resistant Hypertension in Chronic Kidney Disease; AOBP, automated office BP; BP, blood pressure; CKD, chronic kidney disease; eGFR, estimated glomerular filtration; FIDELIO-DKD, Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease; FIDELITY, Finerenone in Chronic Kidney Disease and Type 2 Diabetes: Combined FIDELIO-DKD and FIGARO-DKD Trial; FIGARO-DKD, Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease; [K⁺], potassium concentration; od, once daily; TRH, treatment-resistant hypertension.

Table S2. Confounding Factors in FIDELITY-TRH and the External Comparator (AMBER) Study

	FIDELITY-TRH (n = 624)	AMBER Spironolactone + Patiromer (n = 147)	AMBER Spironolactone + Placebo (n = 148)	Confounding Effect
Study aims	<ul style="list-style-type: none"> The FIDELIO-DKD and FIGARO-DKD trials, and, therefore, FIDELITY- TRH analysis, were designed to maximize detection of benefits of finerenone on hard cardiovascular and kidney outcomes^{10,13,14} 	<ul style="list-style-type: none"> The AMBER study was designed to maximize detection of the benefit of using a potassium-binding agent, patiromer, to increase spironolactone persistence⁹ 		The outcomes are therefore different and cannot be directly compared
Study design	<ul style="list-style-type: none"> The FIDELIO-DKD and FIGARO-DKD studies both comprised a run-in period (during which RASi therapy was optimized) of at least 4 weeks and up to a maximum of 16 weeks, a screening period, and a double-blind treatment period Patients in both studies were randomized 1:1 to receive oral finerenone or matching placebo once daily; with 13,026 patients included in the FIDELITY analysis Double-blind for finerenone with placebo control 	<ul style="list-style-type: none"> The study included a run-in period of up to 4 weeks, a double-blind treatment period of 12 weeks, and a follow-up visit 2 weeks after the 12-week visit or early termination The study randomized 295 patients to receive spironolactone + patiromer (N = 147) or spironolactone + placebo (N = 148) Open label for spironolactone with all patients receiving spironolactone 		Open-label spironolactone may introduce bias with respect to hyperkalemia detection by investigators
Study duration	Median follow-up 3 years (~157 weeks)	12 weeks		End of follow-up analysis cannot be performed; approximations were used to compare the two trials (~17 weeks compared with 12 weeks)
Baseline UACR,	628 (203–1419)	87 (18-467) ^a	73 (189-400) ^a	Likely to impact serum as increased

	FIDELITY-TRH (n = 624)	AMBER Spironolactone + Patiromer (n = 147)	AMBER Spironolactone + Placebo (n = 148)	Confounding Effect
mg/g, median (IQR)				UACR may be associated with increased risk of increased serum [K ⁺] ¹⁰
Female population, n (%)	35%	48%	48%	The female sex is associated with a lower risk of hyperkalemia ^{10,27}
Black population, n (%)	34 (5)	2 (1)	2 (1)	Likely to impact incidence of hyperkalemia as Black population is associated with lower risk of hyperkalemia compared with White population ^{26,27}
Medical history, n (%)				
Diabetes	624 (100)	73 (50)	72 (49)	Diabetes is associated with an increased risk of hyperkalemia ²⁷ and increased SBP ⁷
Heart failure	71 (11)	63 (43)	69 (47)	Heart failure is associated with an increased risk of hyperkalemia ²⁹
Concomitant medications, n (%)				
Beta-blockers	419 (67)	87 (59)	86 (58)	May contribute to SBP-lowering effects observed ⁷ ; beta-blockers have been associated with increased risk of hyperkalemia ²⁸
RAAS inhibitors	624 (100)	147 (100)	147 (99)	RASi may increase the risk of hyperkalemia and acute kidney injury ²⁵ ; FIDELITY-TRH patients received the maximum tolerated dose of RASi whereas the AMBER study protocol did not have a specified requirement for RASi dosing

	FIDELITY-TRH (n = 624)	AMBER Spironolactone + Patiromer (n = 147)	AMBER Spironolactone + Placebo (n = 148)	Confounding Effect
Serum [K ⁺] monitoring frequency	<ul style="list-style-type: none"> Follow-up visits in were conducted at months 1 and 4, then every 4 months thereafter 	<ul style="list-style-type: none"> Visits were scheduled weekly during the first 4 weeks then biweekly during weeks 5-12 	Likely to impact the incidence of discontinuation observed, as a higher incidence of hyperkalemia is observed as serum [K ⁺] monitoring frequency increases ³⁰	

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^a24-hour UACR.