Sodium Zirconium Cyclosilicate and MRA Optimization in Heart Failure With Reduced Ejection Fraction and Hyperkalemia: Main Results From REALIZE-K Randomized Controlled Trial

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On behalf of the REALIZE-K Investigators and Trial Committees

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Disclosures

- Research Grants
  - AstraZeneca, Boehringer Ingelheim, and Pfizer
- Consultant or Advisory Boards
  - 35Pharma, Alnylam, Amgen, Applied Therapeutics, Arrowhead Pharmaceuticals, AstraZeneca, Bayer, Boehringer Ingelheim, Corcept Therapeutics, Cytokinetics, Dexcom, Eli Lilly, Esperion Therapeutics, Imbria Pharmaceuticals, Janssen, Lexicon Pharmaceuticals, Merck (Diabetes and Cardiovascular), Novo Nordisk, Pfizer, Pharmacosmos, Regeneron, Roche, Sanofi, scPharmaceuticals, Structure Therapeutics, Vifor Pharma, and Youngene Therapeutics
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- Other
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Disclosures for Mikhail N. Kosiborod are provided.

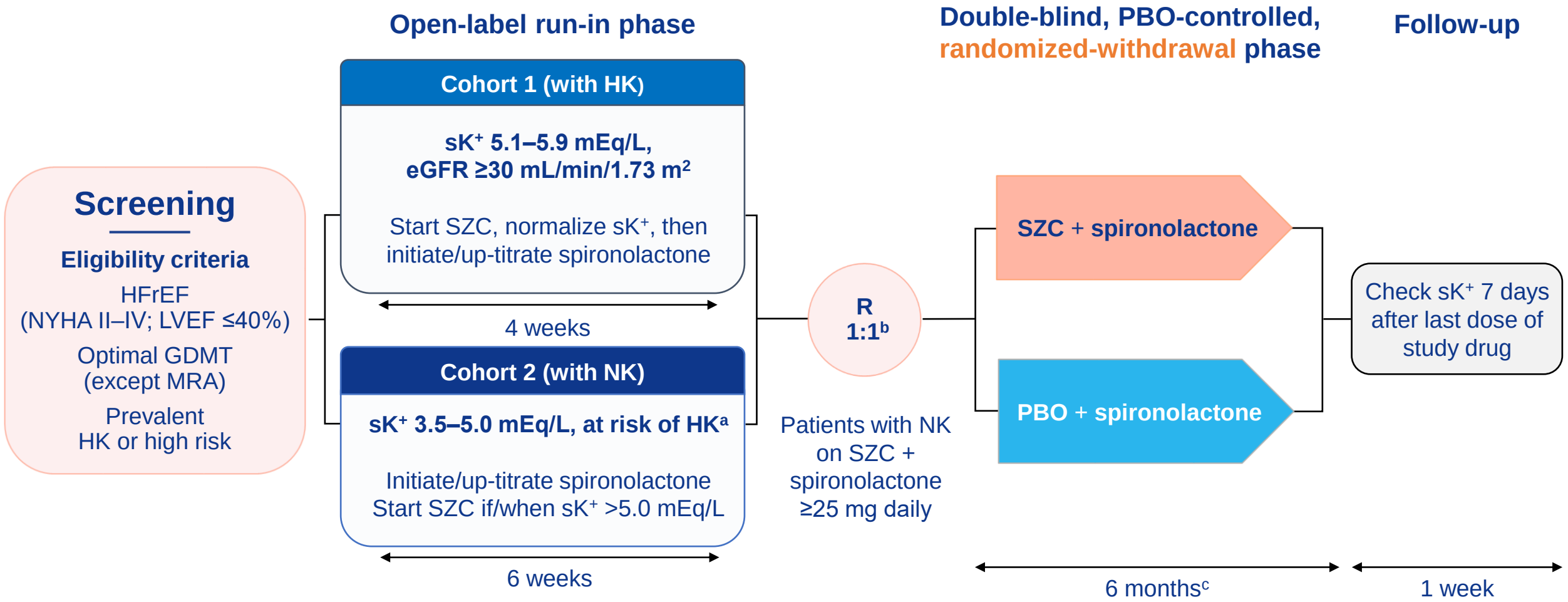
Background

- MRAs reduce the risk of morbidity and mortality in patients with HFrEF but are underused, partly due to HK risk[1]
- The advent of novel potassium binders, including SZC, has introduced the concept of enabling the optimal use of MRA in patients with HFrEF who develop hyperkalemia[2]
- We tested whether SZC enables optimization of the MRA spironolactone in patients with HFrEF and HK

HFrEF, heart failure and reduced ejection fraction; HK, hyperkalemia; MRA, mineralocorticoid receptor antagonist; SZC, sodium zirconium cyclosilicate.

1. Heidenreich PA et al. *J Am Coll Cardiol*. 2022;79:e263–e421. 2. Paolillo S et al. *Eur J Intern Med*. 2024;119:109–117.

Study Design



MRA optimization during run-in phase and maintenance during randomization phase was protocol-mandated

[a]History of HK in the previous 36 months and eGFR ≥30 mL/min/1.73 m^2, or sK^+ 4.5–5.0 mEq/L and eGFR 30–60 mL/min/1.73 m^2, or sK^+ 4.5–5.0 mEq/L and aged >75 years.
[b]Stratified by Cohorts 1 and 2. [c]Visit Weeks: 1, 2, 5, 9, 13, 17, 21, and 25 (Weeks 5–25 included in the primary endpoint). eGFR, estimated glomerular filtration rate; GDMT, guideline-directed medical therapy; HFrEF, heart failure and reduced ejection fraction; HK, hyperkalemia; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NK, normokalemia; NYHA, New York Heart Association; PBO, placebo; R, randomized; sK^+, serum potassium; SZC, sodium zirconium cyclosilicate. Kosiborod, M, Cherney, D, Connelly, K. et al. Sodium Zirconium Cyclosilicate in HFrEF and Hyperkalemia: REALIZE-K Design and Baseline Characteristics. Presented at ESC-HF 2024, Lisbon, Portugal.

Endpoints

Primary

- Percentage with optimal treatment response (NK,[a] spironolactone ≥25 mg/daily, and no rescue therapy since prior visit, Months 1–6 after randomization)

Secondary (tested hierarchically)

- Percentage with NK,[a] on the randomization dose of spironolactone, and no rescue therapy
- Percentage on spironolactone ≥25 mg/daily
- Time to first HK episode (sK^+ >5.0 mEq/L)
- Time to first decrease or discontinuation of spironolactone dose due to HK
- KCCQ-CSS at 6 months

Overall safety

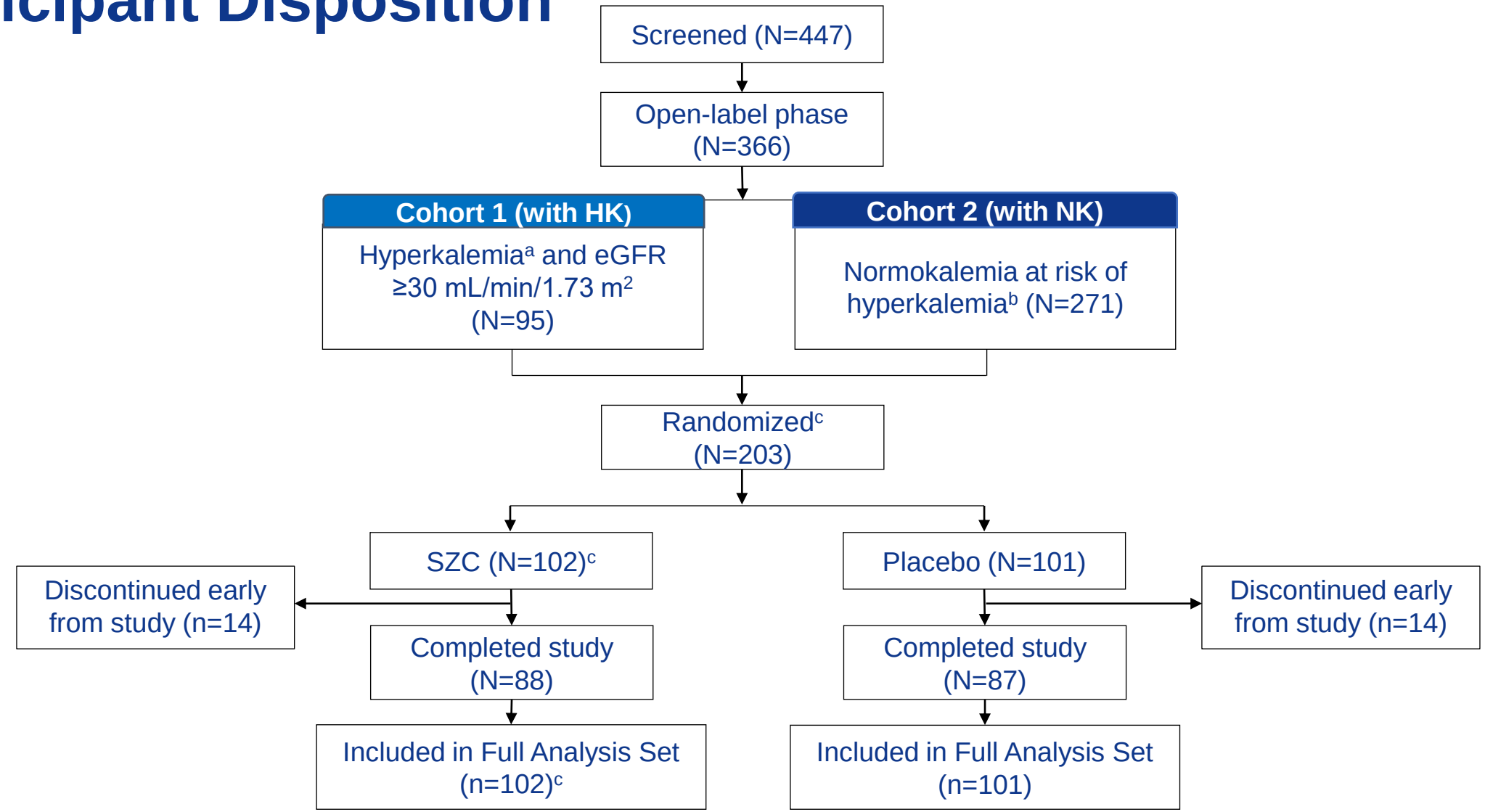
- AEs and SAEs
- Vital signs, physical examination, and laboratory tests

Exploratory

- Time to first occurrence of CV death or worsening HF events[b]
- NTproBNP and daily loop diuretic dose at 6 months post-randomization
- Body weight; systolic blood pressure

[a]NK defined as sK^+ 3.5–5.0 mEq/L. [b]Worsening HF events defined as HF hospitalizations or urgent visits as adjudicated by a centralized clinical events committee blinded to treatment assignment.
AE, adverse event; CV, cardiovascular; HF, heart failure; HK, hyperkalemia; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire-Clinical Summary Score; NK, normokalemia; NTproBNP, N-terminal pro-B-type natriuretic peptide; SAE, serious adverse event; sK^+, serum potassium; SZC, sodium zirconium cyclosilicate.

Participant Disposition



[a]Defined as sK^+ 5.1–5.9 mEq/L. [b]Defined as either a history of sK^+ >5.0 mEq/L within the prior 36 months and eGFR ≥30 ml/min/1.73 m², or sK+ 4.5–5.0 mEq/L with eGFR between 30 and 60 ml/min/1.73 m² or aged >75 years. [c]One participant was randomized in error (in the SZC group) and, therefore, 202 participants received treatment.
eGFR, estimated glomerular filtration rate; sK^+, serum potassium; SZC, sodium zirconium cyclosilicate.

Baseline Characteristics

	SZC (N=102)[a]	Placebo (N=101)
Age, years, median (IQR)	73 (67–79)	69 (63–76)
Sex, male, n (%)	76 (75)	75 (74)
Race, n (%)		
Black or African American	5 (5)	5 (5)
Other	6 (6)	2 (2)
White	91 (89)	94 (93)
Region, n (%)		
Latin America	31 (30)	19 (19)
North America	13 (13)	24 (24)
Europe	58 (57)	58 (57)
Type 2 diabetes, n (%)	27 (27)	25 (25)
Atrial fibrillation, n (%)	36 (35)	36 (36)
Previous HF hospitalization, n (%)	48 (47)	51 (51)
NYHA class, n (%)		
II	85 (83)	85 (84)
III/IV	17 (17)	16 (16)

[a]One participant was randomized in error (in the SZC group), therefore, 202 participants received treatment.
HF, heart failure; IQR, interquartile range; NYHA, New York Heart Association; SZC, sodium zirconium cyclosilicate.

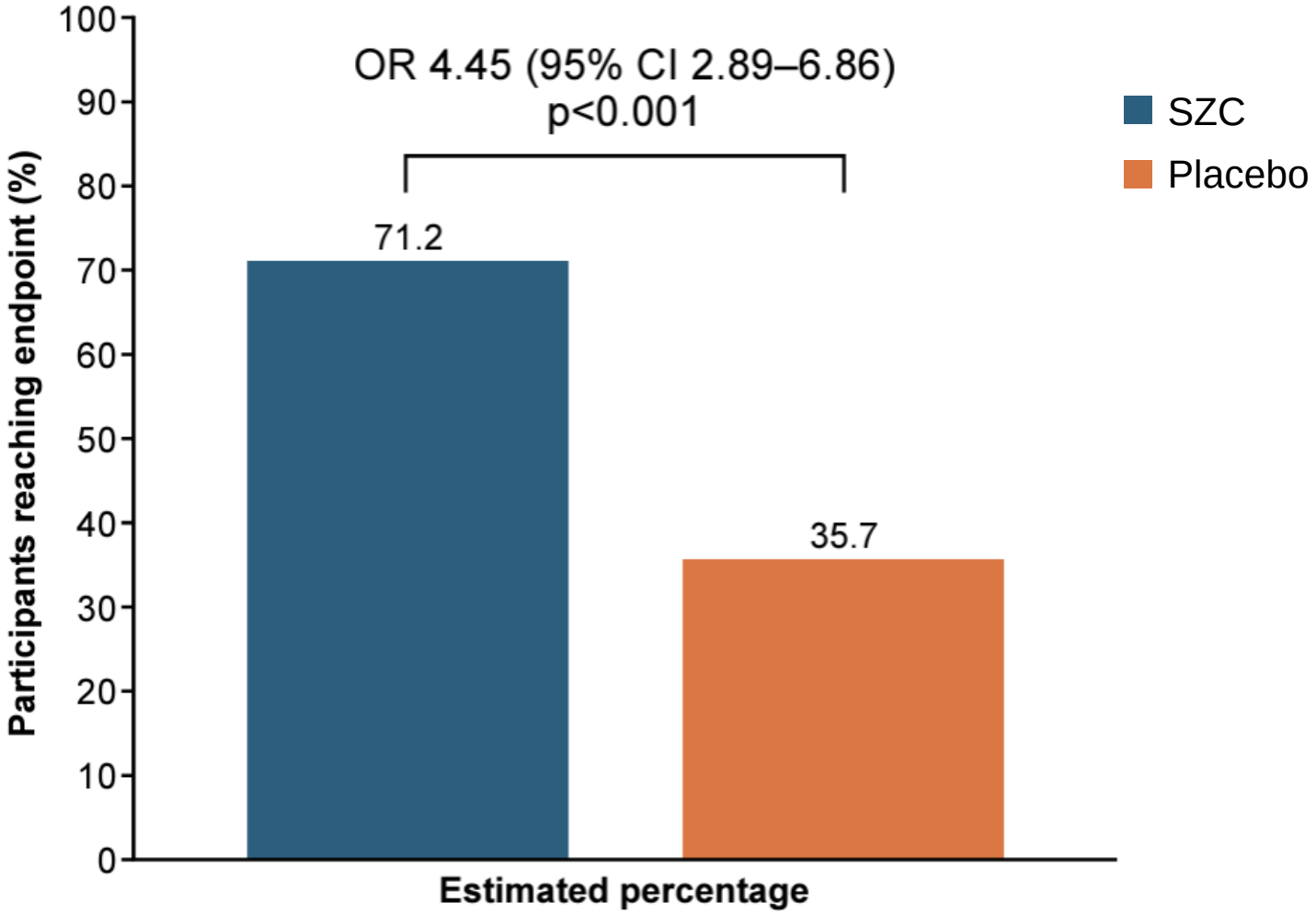
Baseline Characteristics

	SZC (N=102)[a]	Placebo (N=101)
LVEF, %, median (IQR)	33 (28–37)	33 (27–37)
NTproBNP, pg/mL, median (IQR)	1268 (523–3725)	910 (378–2858)
eGFR, mL/min/1.73 m^2, median (IQR)	48 (42–61)	60 (45–74)
Serum K^+, mEq/L, mean (SD)	5.0 (0.5)	5.0 (0.5)
HF therapy, n (%)		
ARNi (sacubitril/valsartan)	63 (62)	67 (66)
ACEi/ARB/ARNi	101 (99)	100 (99)
Beta blockers	96 (95)	98 (97)
SGLT2 inhibitor, n (%)	73 (72)	70 (69)
Low-dose MRA, n (%)	44 (44)	62 (61)
Loop diuretics, n (%)	66 (65)	49 (48)
Spironolactone dose/day at randomization, n (%)		
50 mg	75 (74)	83 (82)

[a]One participant was randomized in error (in the SZC group), therefore, 202 participants received treatment. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor-neprilysin inhibitor; eGFR, estimated glomerular filtration rate; HF, heart failure; IQR, interquartile range; K^+, potassium; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NTproBNP, N-terminal pro-B-type natriuretic peptide; SD, standard deviation; SGLT2, sodium-glucose cotransporter-2; SZC, sodium zirconium cyclosilicate.

Primary Endpoint: Percentage With Optimal Treatment Response

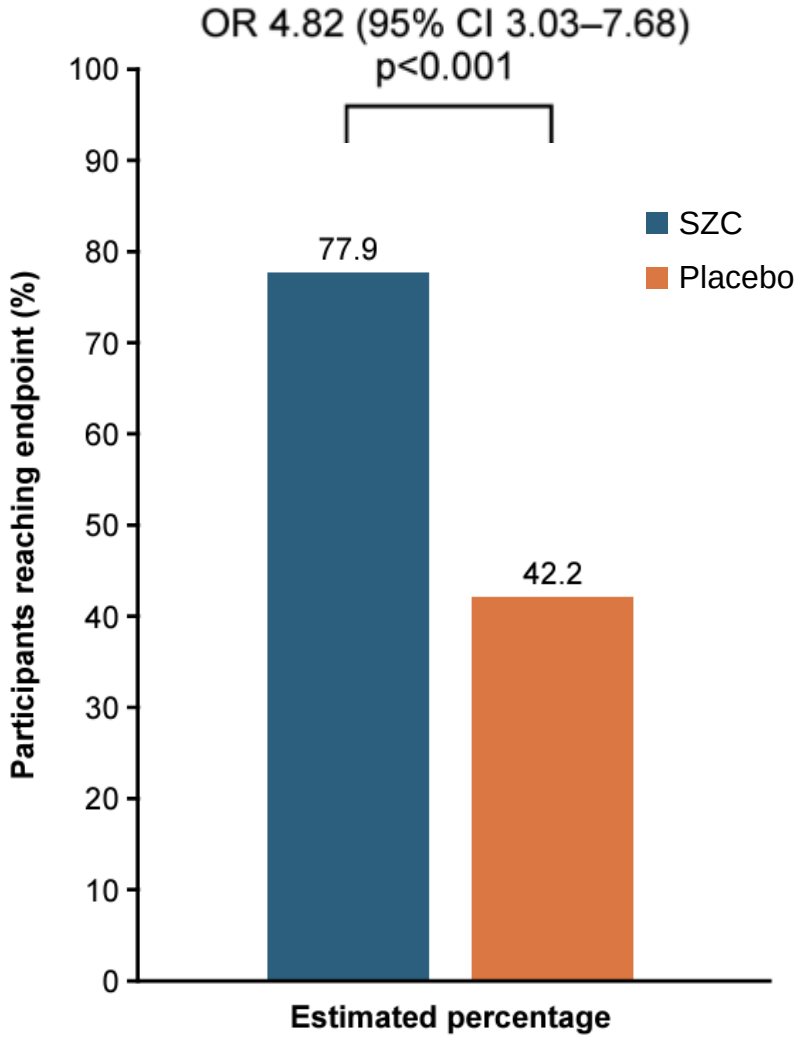
- NK (K^+ 3.5–5.0 mEq/L)
- Spironolactone ≥25 mg/daily
- No rescue therapy since prior visit, Months 1–6



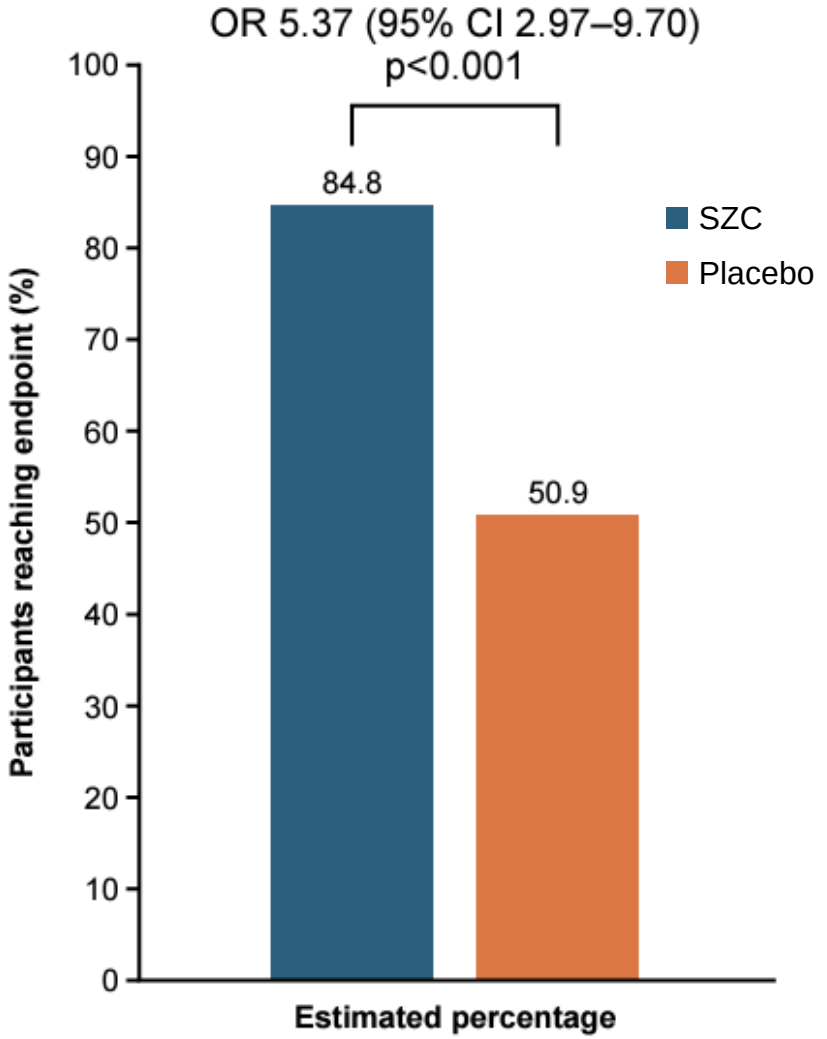
The analysis was performed using a generalized estimating equation model with a binomial family and a log link, a dependent variable of response per visit, fixed independent variables of randomized treatment, participant recruitment country, a per visit indicator variable and open-label period cohort. Each participant was treated as a cluster.
The *P*-value reflects the two-sided z-test. CI, confidence interval; K^+, potassium; NK, normokalemia; OR, odds ratio; SZC, sodium zirconium cyclosilicate.

Sensitivity Analyses of Primary Endpoint

Participants receiving the 15-g dose of SZC (or placebo) at randomization were excluded



A more conservative K^+ threshold to define HK (K^+ ≥5.5 mEq/L rather than >5.0 mEq/L) was used

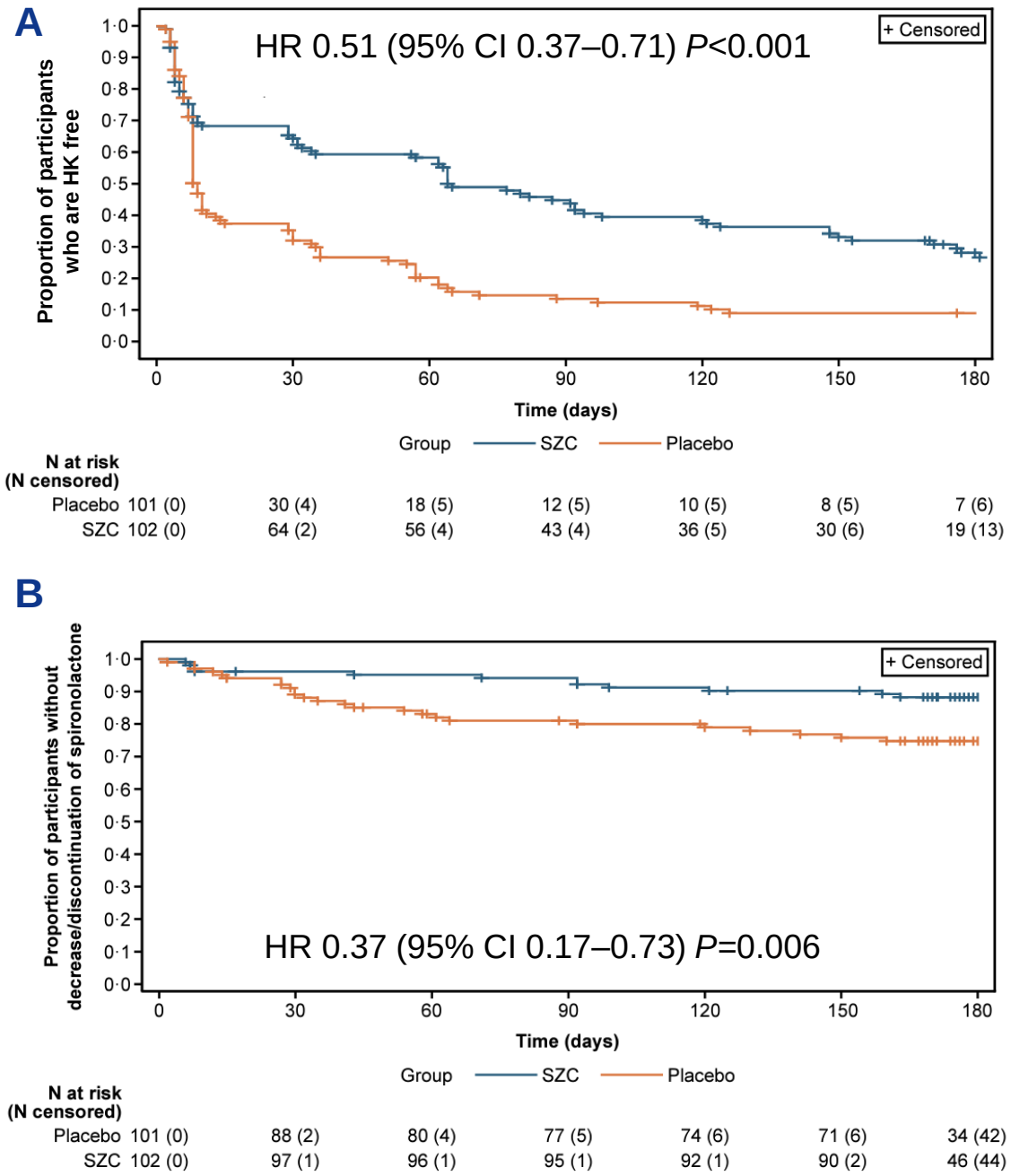


CI, confidence interval; HK, hyperkalemia; K^+, potassium; OR, odds ratio; SZC, sodium zirconium cyclosilicate.

Confirmatory Secondary Endpoints

SZC (vs placebo) improved the first four of five hierarchically tested secondary endpoints

- NK on the randomization dose of spironolactone and without rescue therapy for HK (OR 4.58 [2.78–7.55], *P*<0.001; estimated percentages: 58% vs 23%)
- On spironolactone ≥25 mg/daily dose (OR 4.33 [2.50–7.52], *P*<0.001; estimated percentages 81% vs 50%)
- Time to first HK episode (**A**)
- Time to first decrease or discontinuation of spironolactone dose due to HK (**B**)
- No between-group difference in KCCQ-CSS at 6 months for SZC versus placebo (mean treatment difference −1.01 points [95% CI −6.64 to 4.63], *P*=0.72)



Kaplan–Meier survival curves are truncated at 180 days post-randomization. Analysis of HR was performed using a Cox regression model including randomized treatment group and participant recruitment country, adjusted for the stratification factor (HK vs NK at study entry). Placebo group was used as the reference level in the Cox model.
CI, confidence interval; HK, hyperkalemia; HR, hazard ratio; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire-Clinical Summary Score; N, number of participants; OR, odds ratio;
SZC, sodium zirconium cyclosilicate.

Overall Safety

AEs and SAEs were balanced between groups

	SZC (N=101)	Placebo (N=101)
AEs		
Any AE, n (%)	65 (64)	64 (63)
Any SAE, n (%)	23 (23)	22 (22)
AEs leading to discontinuation, n (%)	6 (6)	6 (6)
SAEs leading to discontinuation, n (%)	3 (3)	2 (2)
Peripheral edema AEs, n (%)	6 (6)	2 (2)
Hypokalemia, n (%)	7 (7)	0 (0)
AE with outcome of death, n (%)	1 (1)	2 (2)
Cardiac failure SAEs, n (%)	12 (12)*	4 (4)
Cardiovascular death, n (%)	1 (1)	1 (1)
Edema questionnaire data[a]		
Peripheral edema, n (%)	22 (22)	16 (16)

* All events of cardiac failure in the SZC group were resolved or resolving at the end of study

Participants with multiple events in the same category were counted only once in that category. Participants with events in more than one category were counted once in each of those categories. Percentages are based on the total numbers of participants in the treatment group (N). [a]An edema questionnaire was completed at 5, 17, and 25 weeks. Participants with multiple peripheral edema events were counted once only. Location of edema is not mutually exclusive, so multiple locations may apply for each participant.
AE, adverse event; SAE, serious adverse event; SZC, sodium zirconium cyclosilicate.

Exploratory and *Post Hoc* Analyses

- Eleven (11%) participants in the SZC and three (3%) in the placebo group had an adjudicated event of CV death or worsening HF (hospitalization or urgent visit; nominal log-rank *P*=0.034)
  - No difference in CV death (one event in each group)
  - More SZC than placebo-treated participants with an adjudicated HF event (n=10 [10%] vs n=2 [2%])
  - In a post hoc exploratory analysis, this difference appeared to be mostly centered among participants with NTproBNP >4000 pg/mL at baseline
- NTproBNP at 6 months post-randomization was somewhat higher with SZC versus placebo (1.26 [95% CI 0.99–1.61], nominal *P*=0.061)
- No significant between-group differences in dose of loop diuretics, body weight or systolic blood pressure at 6 months

N numbers represent the numbers of participants with available baseline NTproBNP data.
CI, confidence interval; CV, cardiovascular; HF, heart failure; NTproBNP, N-terminal pro-B-type natriuretic peptide; SZC, sodium zirconium cyclosilicate.

Summary

Efficacy

- In participants with symptomatic HFrEF and HK, SZC led to large improvements in optimizing the use and dose of MRA and K^+ levels, and reduced the risk of HK and down-titration or discontinuation of spironolactone

Safety

- No imbalance in total AEs and SAEs
- The number of HF*, edema, and hypokalemia events was relatively small, but more participants had such events with SZC than placebo
  - In a *post hoc*, exploratory analysis of HF events, this difference appeared to be mostly centered among participants with very high NTproBNP levels at baseline

Clinical considerations

- SZC effectively enables more optimal use of MRA in patients with HFrEF
- Although underpowered for clinical outcomes, more participants had HF events with SZC than placebo despite the more optimal use of spironolactone, which should be factored into clinical decision making

*All events of cardiac failure in the SZC group were resolved or resolving at the end of study.

AE, adverse event; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; HK, hyperkalemia; K^+, potassium; MRA, mineralocorticoid receptor antagonist; NTproBNP, N-terminal pro-B-type natriuretic peptide; SAE, serious adverse event; SZC, sodium zirconium cyclosilicate.

Thank you

- Thank you to the REALIZE-K Participants, Investigators, and Sponsor
  - Steering Committee: David Cherney; Akshay Desai; Mikhail Kosiborod; Mark Petrie; Jeffrey Testani; Subodh Verma
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