Finerenone in Heart Failure with Mildly Reduced or Preserved Ejection Fraction: The FINEARTS-HF Trial

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on behalf of the FINEARTS-HF Investigators

FINEARTS-HF

FINerenone trial to investigate **E**fficacy and s**A**fety superio**R** to placebo in pa**T**ient**S** with **H**eart **F**ailure

Rationale

- Despite the availability of several therapeutic options in heart failure with mildly reduced or preserved ejection fraction (HFmrEF or HFpEF), including SGLT2 inhibitors, there remains a high unmet need in this population[1,2,3].

- Steroidal mineralocorticoid receptor antagonists (spironolactone, eplerenone) reduce morbidity and mortality in patients with heart failure and reduced ejection fraction; their efficacy in those with HFmrEF or HFpEF has not been definitively established[4,5].

- While spironolactone did not reduce the primary endpoint in the TOPCAT trial, post hoc analyses revealed that a substantial proportion of enrolled patients outside of the Americas may not have had heart failure and probably did not take investigational therapy[6,7]. MRAs are not currently recommended in ESC Guidelines for HFpEF.

- Finerenone is a non-steroidal MRA which, compared with steroidal MRAs, is more selective for the MR receptor, has a shorter half-life, and has a more balanced distribution between the heart and the kidney

1. Solomon et al, NEJM 2019 2. Anker et al. NEJM 2021 3. Solomon et al NEJM 2022 4. Pitt et al. NEJM 1999; 5. Zannad et. al. NEJM 2011 6. Pitt et al. NEJM 2013; 7. Pfeffer et al. Circulation. 2013

FINEARTS-HF Study Design

Randomized, double-blind, placebo-controlled trial testing the hypothesis that finerenone would reduce cardiovascular death and total worsening heart failure events in patients with heart failure and mildly reduced or preserved ejection fraction

Key Inclusion Criteria

- **Symptomatic HF (NYHA class II-V) with LVEF ≥ 40%**
- **Hospitalized, recently hospitalized, or ambulatory**
- **Elevated natriuretic peptide levels**
- **Structural heart disease (LA Enlargement or LVH)**
- **Diuretics in the 30d prior to randomization**

Key Exclusion Criteria

- **Potassium > 5.0 mmol/L; eGFR <25 mL/min/1.73 m²**
- **MRA use 30d prior to randomization**
- **History of peripartum, chemotherapy induced, or infiltrative cardiomyopathy (e.g., amyloidosis)**
- **Alternative causes of signs or symptoms**

1:1 Randomization

Finerenone 10, 20 or 20, 40 mg *dosing based on eGFR: ≤60 max dose 20 mg, >60, max dose 40 mg*

N = 6,001 validly randomized

Uptitrate to maximally tolerated dose if K+<5.0mmol/L and eGFR decrease <30%

Matching Placebo

Visits: Month 1, then 3-monthly for first 12 months, 4-monthly visits thereafter with telephone contact in between

Study Endpoints

Primary Endpoint

- CV death and total HF events (hospitalizations/urgent visits)

Secondary Endpoints

- Total HF events
- KCCQ-TSS at 6,9, and 12 months
- NYHA class at 12 months
- Renal composite endpoint
- All-cause mortality

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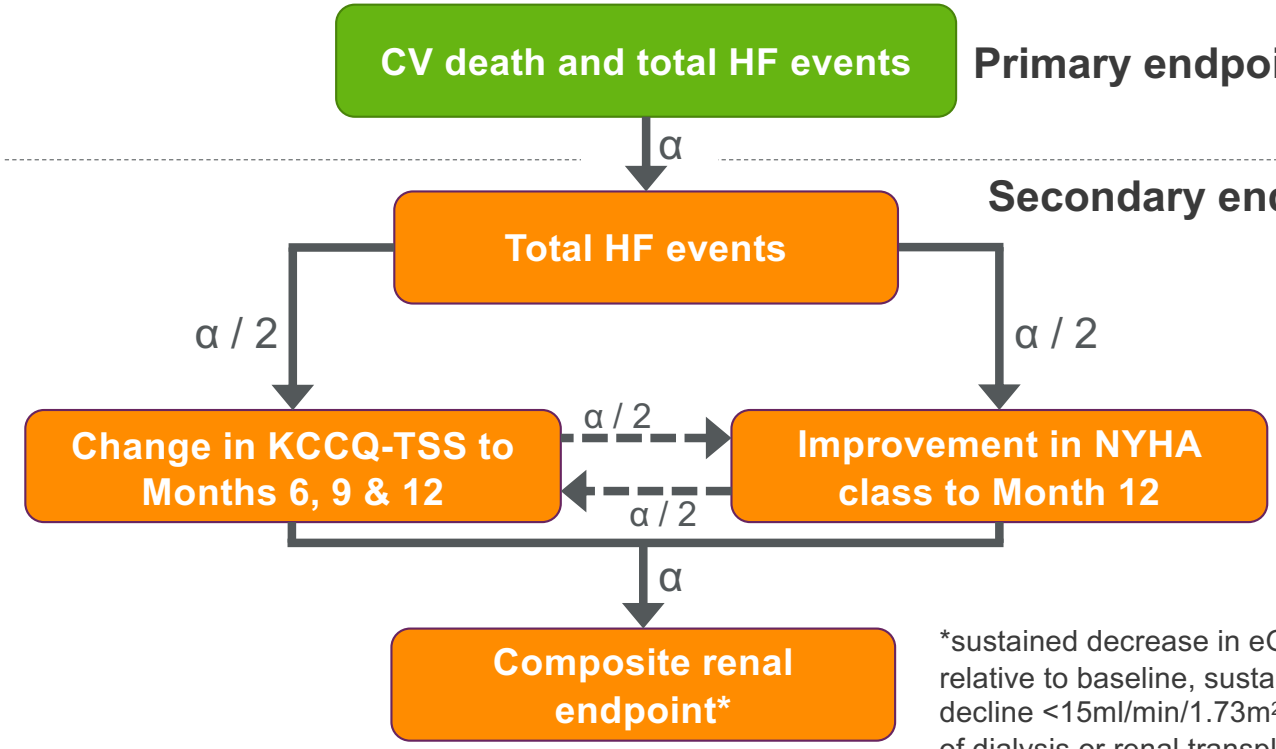
Endpoints and Analysis Plan



All-cause mortality#

#ACM is tested at α=0.05 outside the formal testing strategy

*sustained decrease in eGFR ≥50% relative to baseline, sustained eGFR decline <15ml/min/1.73m^2, initiation of dialysis or renal transplantation

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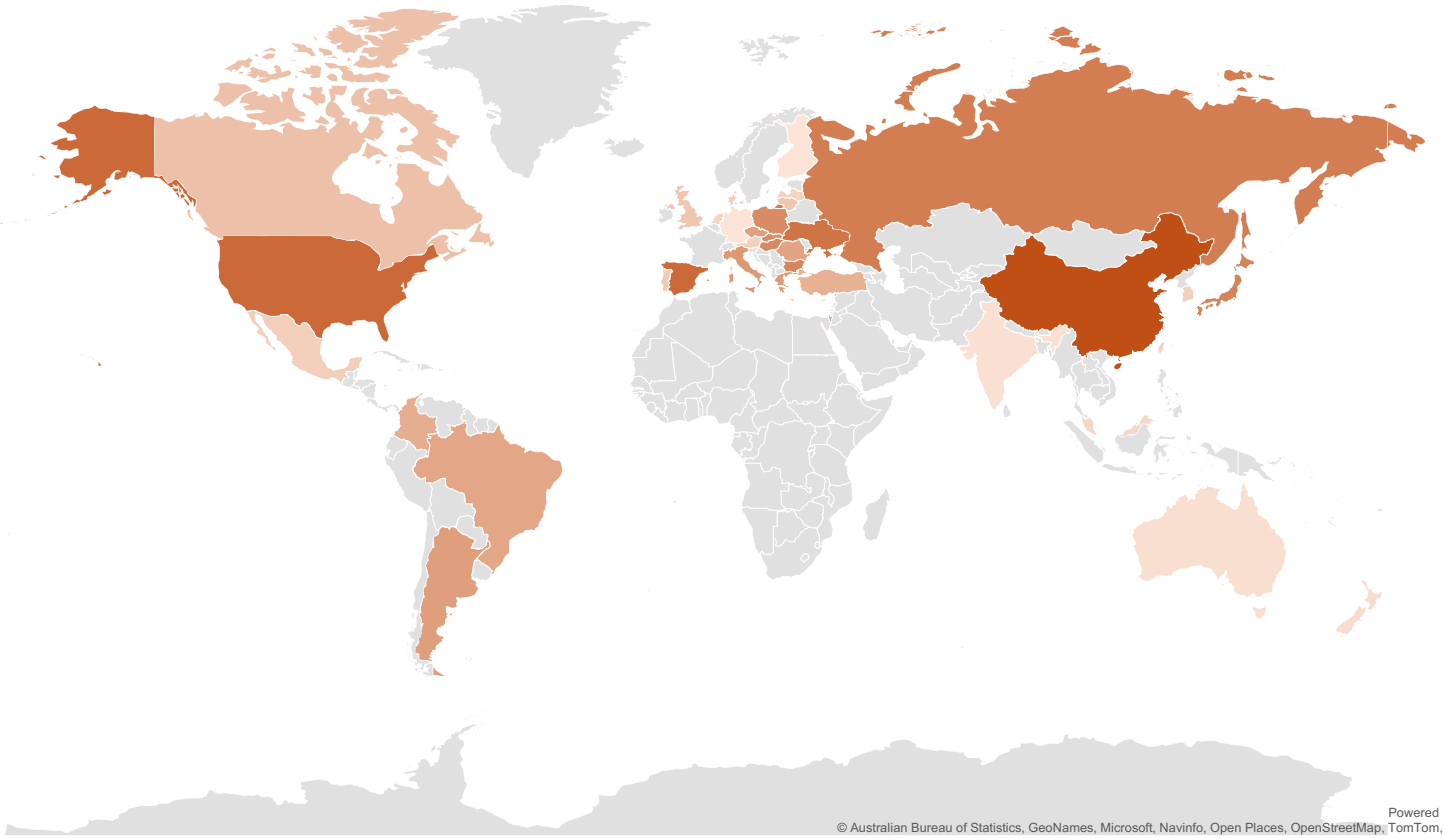
Global randomization across 635 sites in 37 countries



Country	Enrollment (# of Patients)
China	428
USA	355
Spain	353
Ukraine	327
Russian Federation	300
Japan	286
Bulgaria	275
Hungary	267
Slovakia	262
Poland	259
Italy	227
Greece	217
Argentina	211
Czechia	206
Romania	193
Brazil	185
Israel	181
Colombia	167
Turkey	159
Canada	116
Lithuania	100
United Kingdom	99
Portugal	88
Denmark	79
Mexico	78
Republic of Korea	74
Austria	73
Taiwan	69
Latvia	65
Netherlands	64
Malaysia	57
Hong Kong	41
New Zealand	40
Australia	32
India	28
Germany	20
Finland	20

# of Participants Enrolled

20 428

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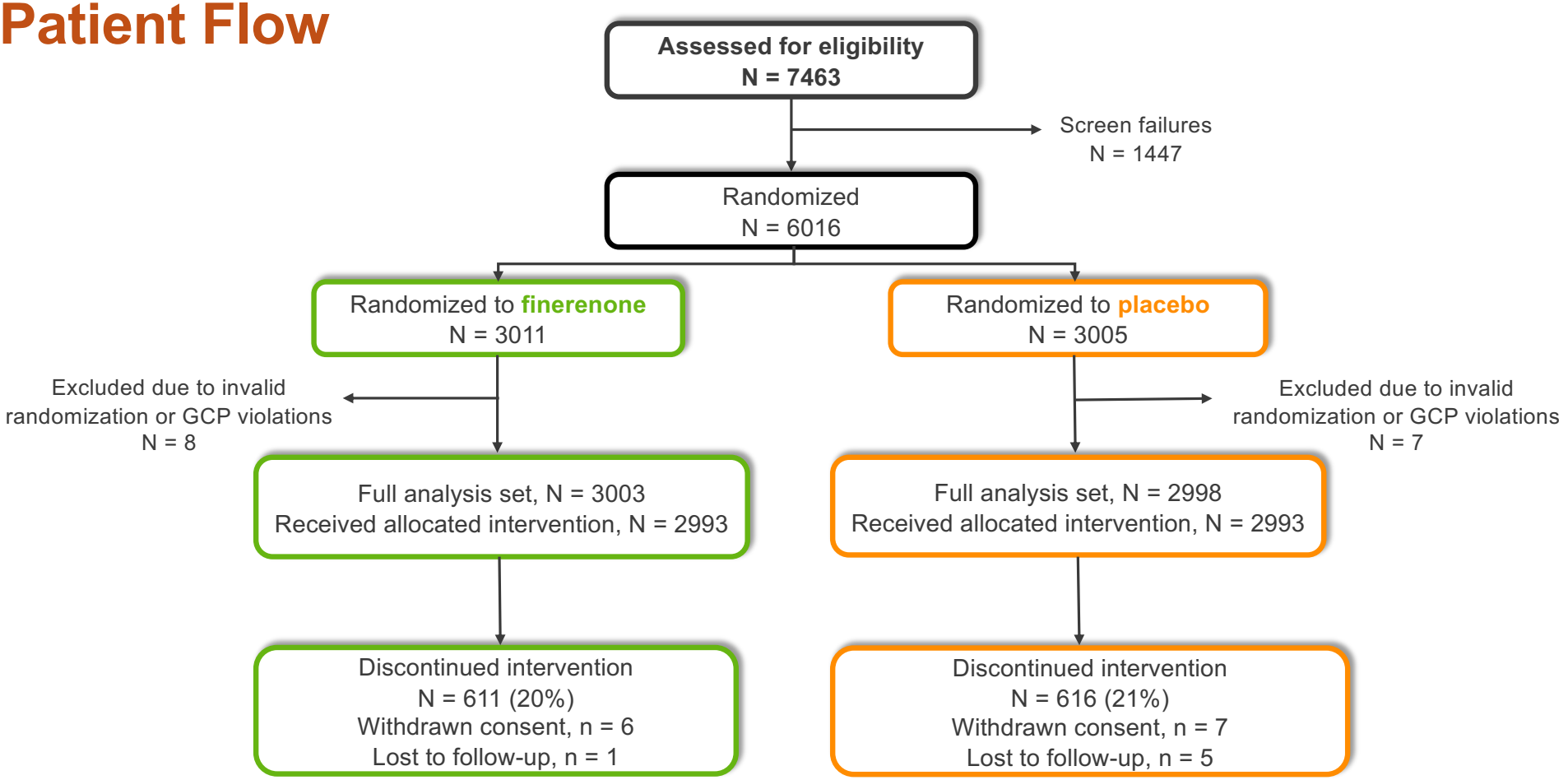
Patient Flow



GCP, good clinical practice

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Baseline Characteristics

Well-balanced between treatment groups

	Finerenone N = 3003	Placebo N = 2998
Age	72±10	72±10
Female Sex	45%	46%
Race		
Asian	17%	17%
Black	2%	1%
Other	3%	3%
White	79%	79%
Region		
Asia	16%	16%
Eastern Europe	44%	44%
Latin America	11%	11%
North America	8%	8%
Western Europe, Oceania and Others	21%	21%
NYHA class		
II	69%	69%
III	30%	30%
IV	1%	1%
KCCQ-TSS	68±24	67±24
LVEF (%)	53±8	53±8
Systolic Blood Pressure (mmHg)	130±15	129±15

	Finerenone N = 3003	Placebo N = 2998
NT-proBNP (ng/L) (median)	1052 [467,1937]	1028 [433,1963]
eGFR (mL/min/1.73m²)	62±19	62±20
eGFR < 60	48%	48%
UACR (mg/g)	18 [7,67]	19 [7,66]
Prior HF Hospitalization	60%	61%
History of LVEF <=40%	5%	4%
Type II Diabetes	41%	41%
Atrial Fibrillation on ECG	38%	38%
History of Hypertension	88%	90%
History of Myocardial Infarction	26%	25%
Loop Diuretic	87%	87%
Beta-blocker	85%	85%
ACE Inhibitor	36%	36%
ARB	35%	35%
ARNI	9%	9%
Calcium Channel Blockers	32%	34%
SGLT2 Inhibitor	13%	14%

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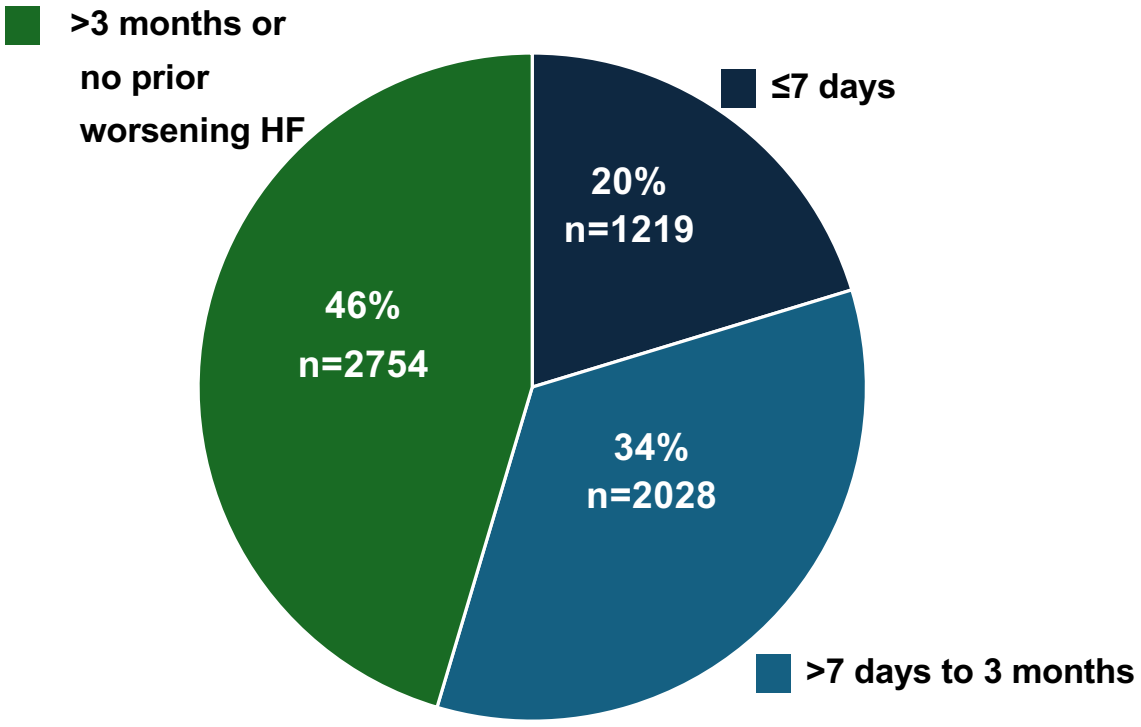
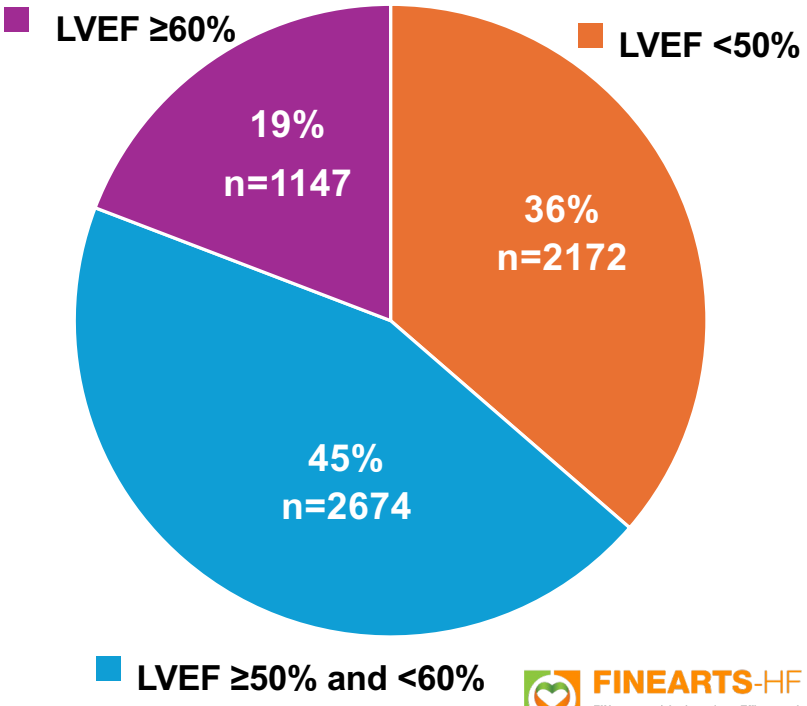
Randomization timing relative to the most recent worsening HF event and LVEF status on randomization

20% of participants were randomized during or within 7 days of a worsening HF event



Mean LVEF status on randomization was 53% across both treatment arms



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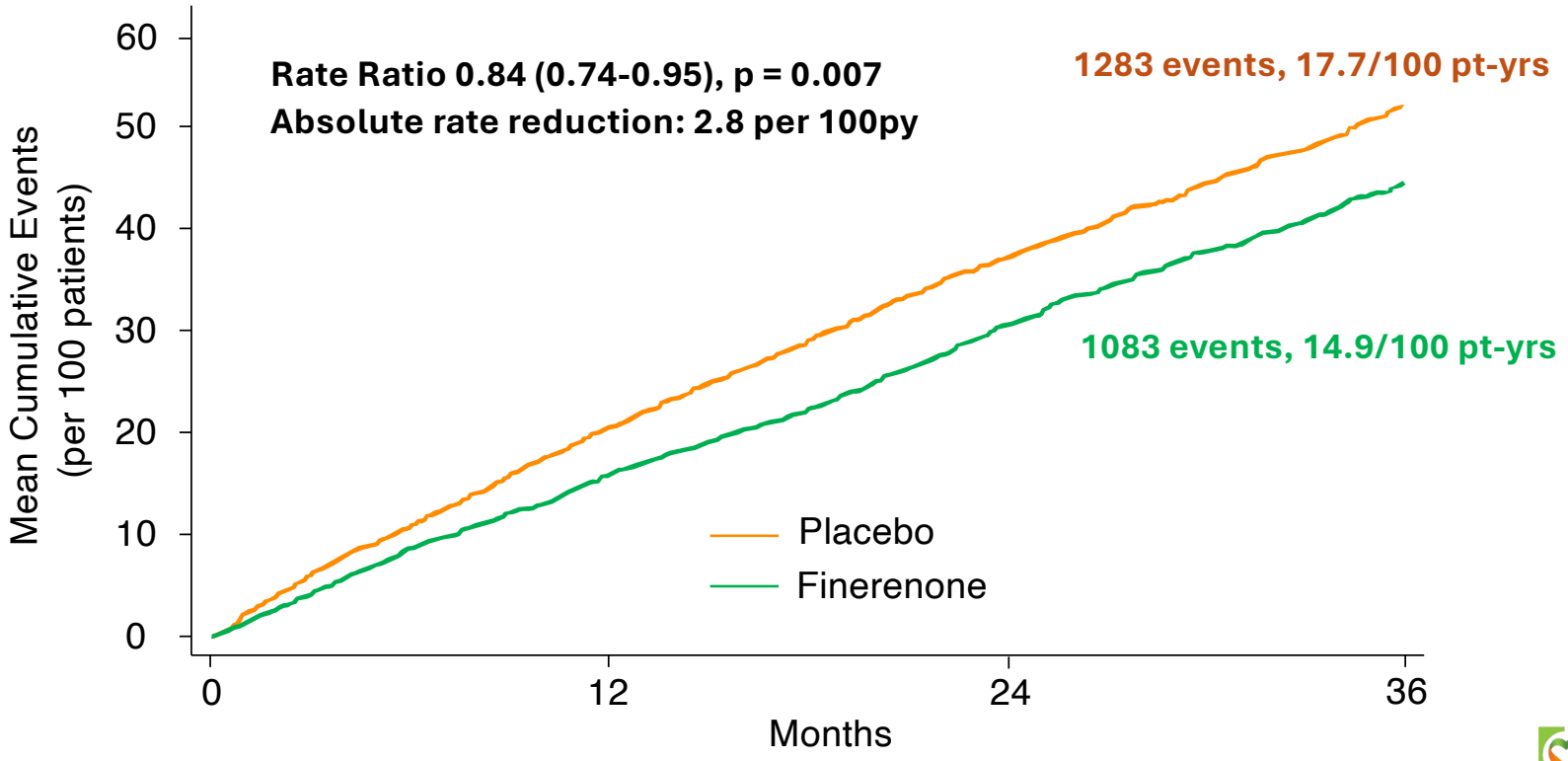
Primary Endpoint: CV Death and Total HF Events

Finerenone reduced cardiovascular death and total worsening heart failure events over median follow-up of 32 months



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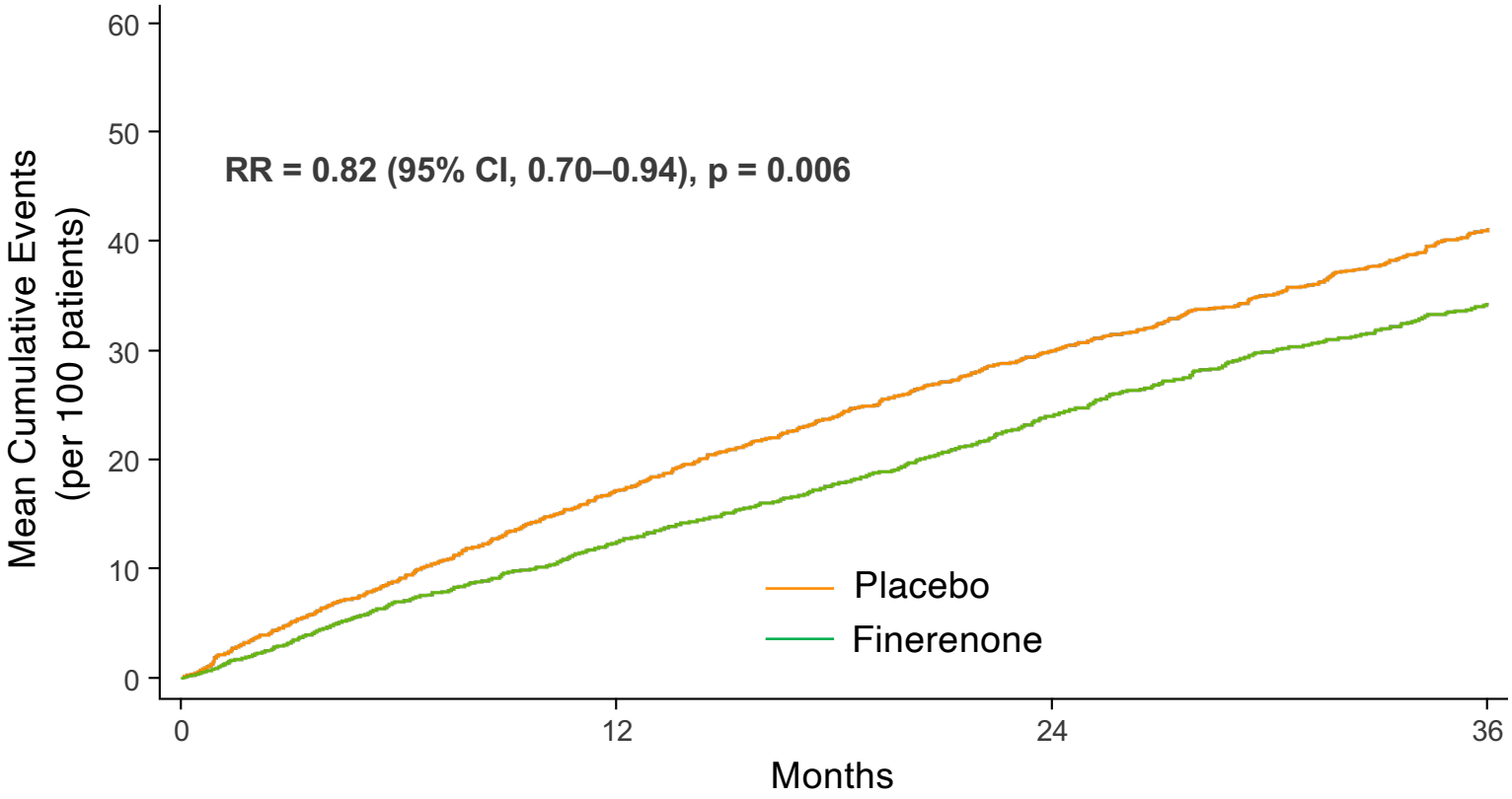
Secondary Endpoint: Total HF Events



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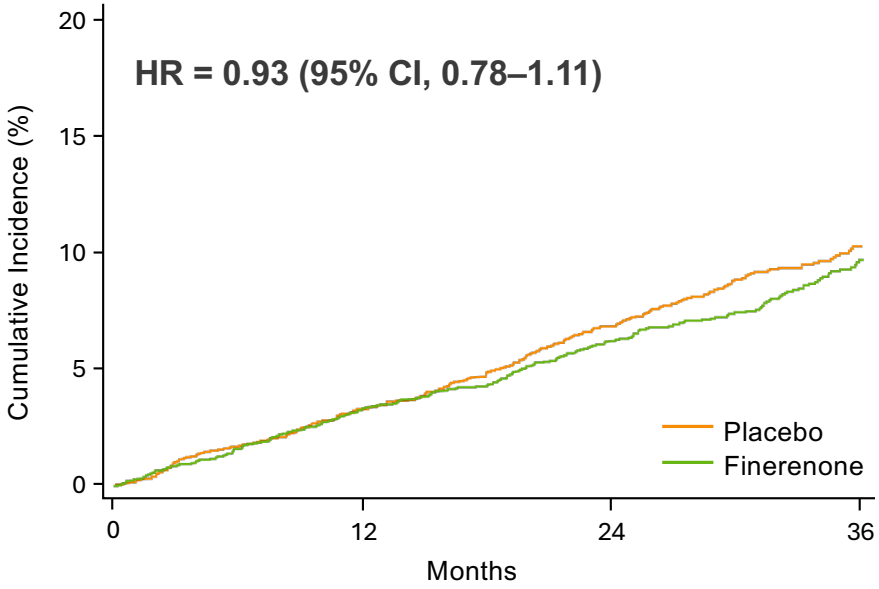
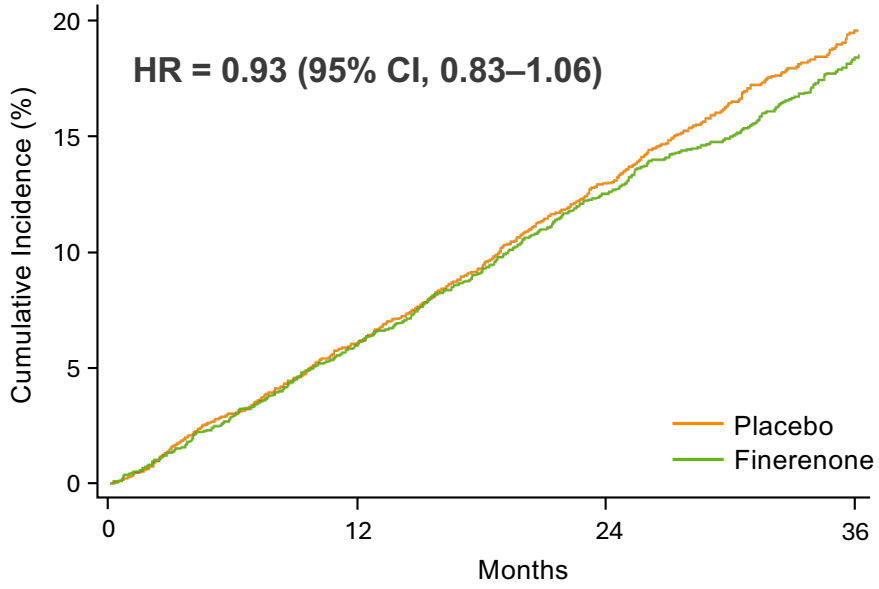
Cardiovascular Death



All-Cause Death



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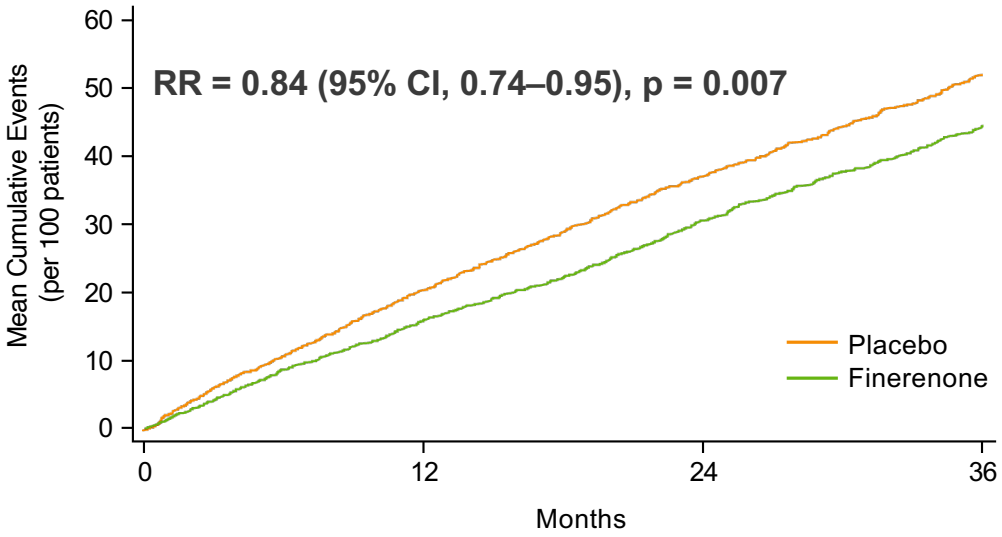
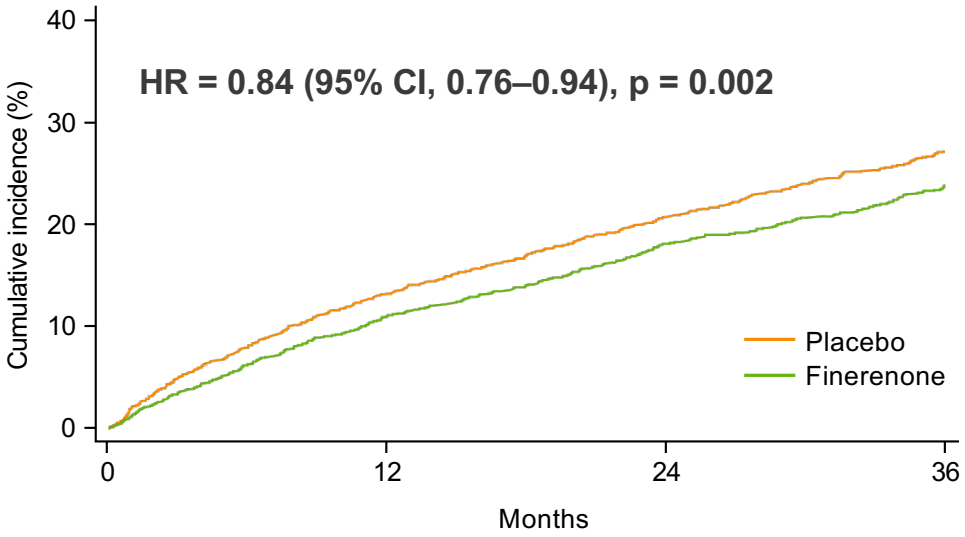
CV Death and Total HF Events

Primary Endpoint



CV Death or First HF Event

Prespecified Sensitivity Analysis



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Prespecified Subgroups for Primary Outcome

Consistent treatment effects across all pre-specified subgroups, including ejection fraction and SGLT2-inhibitor use

Category	Finerenone Events	Placebo Events	RR (95% CI)
Age (years)			
≤ median	468	623	0.76 (0.63–0.92)
> median	615	660	0.92 (0.77–1.09)
Gender			
Male	632	691	0.88 (0.74–1.04)
Female	451	592	0.78 (0.65–0.95)
Race			
White	809	986	0.82 (0.71–0.95)
Black	29	22	0.98 (0.37–2.62)
Asian	211	218	0.96 (0.72–1.29)
Other	34	57	0.60 (0.26–1.42)
BMI			
< 30 kg/m^2	586	648	0.88 (0.74–1.05)
≥ 30 kg/m^2	486	632	0.79 (0.66–0.95)
LVEF			
< 60%	877	1061	0.82 (0.71–0.94)
≥ 60%	206	222	0.94 (0.70–1.26)
Region			
W Eur, Oce & Others	322	395	0.82 (0.64–1.06)
Eastern Europe	322	389	0.83 (0.67–1.03)
Asia	211	218	0.95 (0.71–1.27)
North America	122	118	0.98 (0.67–1.45)
Latin America	106	163	0.65 (0.43–0.98)
NYHA Class			
II	646	741	0.86 (0.73–1.02)
III/IV	437	542	0.79 (0.65–0.96)
Index HF Events			
≤ 7 days	270	372	0.74 (0.57–0.95)
> 7 days to ≤ 3 months	404	492	0.79 (0.64–0.97)
> 3 months or no prior HFE	409	419	0.99 (0.81–1.21)

Category	Finerenone Events	Placebo Events	RR (95% CI)
SBP (mmHg)			
≤ median	608	740	0.85 (0.72–1.01)
> median	475	543	0.84 (0.69–1.02)
eGFR			
< 60 mL/min/1.73m^2	727	796	0.91 (0.78–1.07)
≥ 60 mL/min/1.73m^2	356	487	0.72 (0.59–0.88)
Potassium			
≤ 4.5 mmol/L	714	875	0.81 (0.69–0.95)
> 4.5 mmol/L	369	408	0.91 (0.74–1.11)
NT-proBNP (pg/mL)			
≤ median	266	342	0.78 (0.62–0.99)
> median	782	918	0.83 (0.71–0.96)
UACR			
< 30 mg/g	429	518	0.81 (0.67–0.97)
≥ 30 mg/g	601	705	0.88 (0.74–1.05)
ACEi, ARB or ARNI			
Yes	795	951	0.83 (0.72–0.96)
No	288	332	0.85 (0.66–1.11)
SGLT-2i			
Yes	176	234	0.83 (0.60–1.16)
No	907	1049	0.85 (0.74–0.98)
Atrial Fibrillation per ECG			
Yes	521	621	0.80 (0.66–0.97)
No	562	662	0.85 (0.72–1.01)
Diabetes Mellitus			
Yes	524	638	0.83 (0.69–1.00)
No	559	645	0.85 (0.71–1.01)

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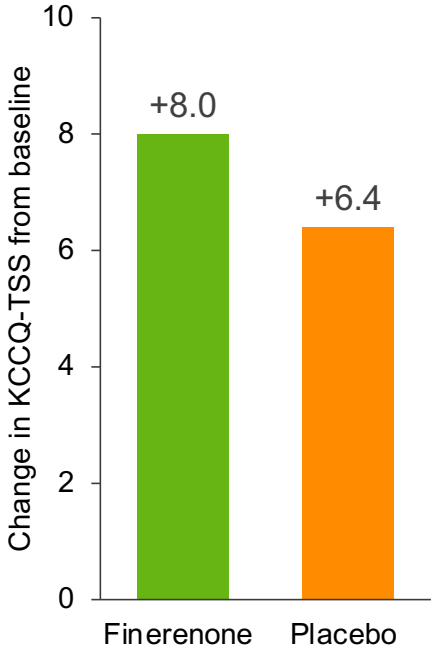
Change in KCCQ-TSS

6, 9, 12 Months

Improvement in Symptom Burden

Between-arm difference:+1.6 (0.8–2.3)

P<0.001

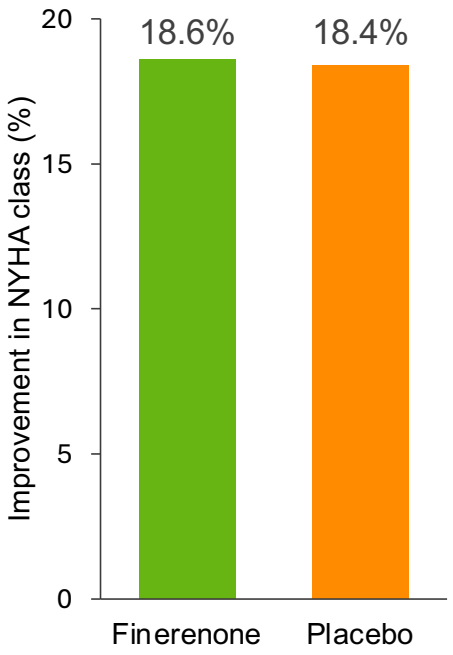


Improvement in NYHA Class

At 12 Months

No improvement in NYHA Class

OR 1.01 (95% CI, 0.88–1.15)



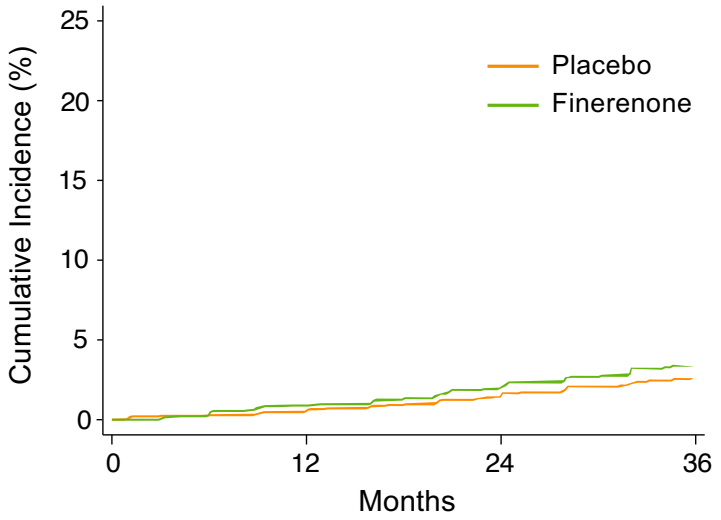
Renal Composite Outcome

Small number of Events; No significant difference

Finerenone events 75 (2.5%)

Placebo events 55 (1.8%)

HR 1.33 (95% CI, 0.94-1.89)



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Safety

Treatment Emergent Safety Outcome	Finerenone (N=2993)	Placebo (N=2993)
Any Serious Adverse Event (SAE)	38.7%	40.5%
Serum creatinine ≥3.0 mg/dl	2.0%	1.2%
Serum potassium		
>5.5 mmol/l	14.3%	6.9 %
>6.0 mmol/l	3.0 %	1.4 %
<3.5 mmol/l	4.4 %	9.7 %
Investigator-reported hyperkalemia	9.7%	4.2%
Leading to hospitalization	0.5%	0.2%
Leading to death	0%	0%
Systolic blood pressure <100 mmHg	18.5%	12.4%

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Conclusions

- Among patients with heart failure and a mildly reduced or preserved ejection fraction, finerenone reduced the risk of the primary composite outcome of cardiovascular death and total heart failure events, reduced total heart failure events, and improved overall health status
- These findings were consistent across prespecified subgroups, including across LVEF and in those on SGLT2 inhibitors
- Hyperkalemia was more common, and hypokalemia less common, in those receiving finerenone
- These data support the use of finerenone in patients with heart failure with mildly reduced or preserved ejection fraction

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ORIGINAL ARTICLE

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