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BRIEF REPORT

Time to Significant Benefit of Finerenone in Patients With Heart Failure

Muthiah Vaduganathan, MD, MPH,[a] Brian L. Claggett, PhD,[a] Akshay S. Desai, MD, MPH,[a] Pardeep S. Jhund, MD, PhD,[b] Carolyn S.P. Lam, MD, PhD,[c] Michele Senni, MD,[d] Sanjiv J. Shah, MD,[e] Adriaan A. Voors, MD, PhD,[f] Faiez Zannad, MD, PhD,[g] Bertram Pitt, MD,[h] John JV. McMurray, MD,[b] Scott D. Solomon, MD[a]

The rapidity with which a heart failure (HF) therapy might stabilize health status and improve clinical events may be of particular interest to patients and clinicians. Mineralocorticoid receptor antagonists (MRAs) have traditionally been viewed to modify long-term pathways of disease progression such as end-organ fibrosis and hypertrophy through alteration of intracellular genomic signaling.[1] However, MRAs may additionally influence early pathways of risk by potentiating natriuresis, mitigating inflammatory responses and endothelial dysfunction, and altering hemodynamics.[1] The nonsteroidal MRA finerenone was recently shown to reduce risks of cardiovascular death and worsening HF events among patients with HF with mildly reduced or preserved ejection fraction.[2] In this prespecified analysis of the FINEARTS-HF (Finerenone Trial to Investigate Efficacy and Safety Superior to Placebo in Patients With Heart Failure; NCT04435626), we evaluated the timing of first statistical significance of finerenone in reducing clinical events.

METHODS

As previously described and reported,[2,3] FINEARTS-HF was a global, multicenter randomized clinical trial of finerenone (titrated to 20 mg or 40 mg once daily) vs matching placebo among symptomatic patients with HF and left ventricular ejection fraction ≥40%. Participants could have been enrolled during an episode of worsening HF, after a recent worsening HF event, or while ambulatory. All participants provided explicit informed consent, and the study protocol was approved by the Institutional Review Boards or Ethics Committees at all participating sites.

The primary endpoint was cardiovascular death and total (first and recurrent) worsening HF events. Participants who did not experience a primary endpoint during follow-up were censored at the date of their last contact or date of noncardiovascular death. Time to first cardiovascular death or worsening HF event was a prespecified sensitivity analytic endpoint, and total worsening HF events alone was a secondary endpoint. All deaths and potential HF events were adjudicated by an independent Clinical Events Committee. We iteratively estimated treatment effects on these endpoints with truncated follow-up at every day postrandomization. For instance, a truncated model at day 30 considered clinical events in follow-up that had accrued up until and including day 30. Total events were analyzed

From the [a]Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA; [b]University of Glasgow, Glasgow, Scotland, United Kingdom; [c]National Heart Centre Singapore and Duke-National University of Singapore, Singapore; [d]University of Milano-Bicocca, Papa Giovanni XXIII Hospital, Bergamo, Italy; [e]Northwestern University Feinberg School of Medicine, Chicago, Illinois, USA; [f]University of Groningen, Groningen, the Netherlands; [g]University of Lorraine, Nancy, France; and the [h]University of Michigan, Ann Arbor, Michigan, USA.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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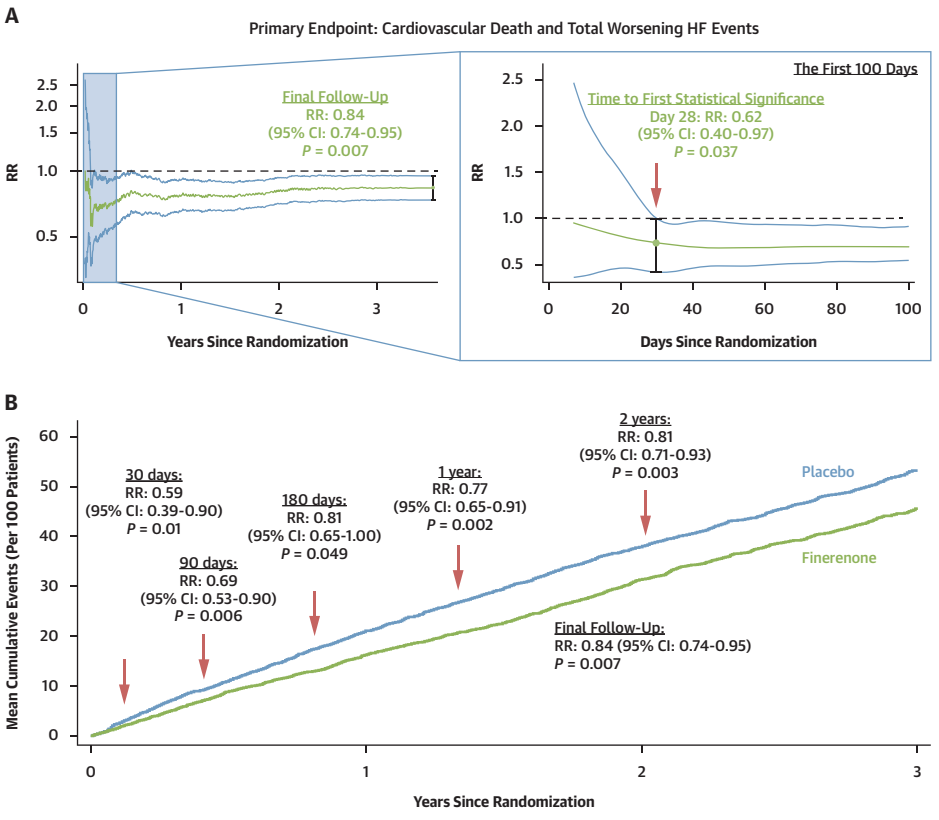
FIGURE 1 Time to First Statistical Significance and Treatment Effects at Multiple Time Points for the Primary Endpoint of FINEARTS-HF



(A) Time to first statistical significance for the primary endpoint in the FINEARTS-HF (Finerenone Trial to Investigate Efficacy and Safety Superior to Placebo in Patients With Heart Failure) trial. Rate ratios (RRs) and 95% CIs based on models with truncated follow-up at every day postrandomization for the primary endpoint of cardiovascular death and total worsening heart failure (HF) events in the FINEARTS-HF trial. A closer view of the first 100 days postrandomization is also displayed after applying a locally weighted scatterplot smoothing procedure. (B) Treatment effects on the primary endpoint at multiple time points in follow-up in the FINEARTS-HF trial. Treatment effects are summarized as RR (95% CI).

using the semiparametric proportional rates method of Lin et al,[4] and first events were analyzed using a Cox proportional hazards model. All models were stratified by geographic region and baseline left ventricular ejection fraction (<60%, ≥60%). Statistical analyses were conducted using STATA version 18 (StataCorp). Two-sided *P* values <0.05 were considered statistically significant. No adjustments for multiple testing were performed.

DATA AVAILABILITY. Data will be made available to qualified scientific and medical researchers through the Vivli website. All requests will be reviewed by an independent scientific review panel and data provided according to the conditions laid out on the Our Members, Bayer webpage of the Vivli website.

RESULTS

Overall, 6,001 participants were validly randomized across 635 sites in 37 countries from September 2020 to January 2023. Median age was 73 years (Q1-Q3: 66-79 years) and 2,732 (45.5%) were women. During 2.6 years follow-up, 1,083 total primary events (14.9 per 100 patient-years) occurred in the finerenone arm compared with 1,283 events (17.7 per 100 patient-years) in the placebo arm yielding a final rate ratio (RR) of 0.84 (95% CI: 0.74-0.95; $P = 0.007$).

Figure 1A displays the time course of clinical benefit with finerenone on the primary endpoint. First nominal statistical significance for the primary endpoint was observed on day 28 (RR: 0.62; 95% CI: 0.40-0.97; $P = 0.037$). Statistical significance was

sustained thereafter in follow-up except on 2 specific days in which the upper bounds of the CI slightly crossed unity ($P = 0.054$ on day 42 and $P = 0.057$ on day 179). First statistical significance was also attained on day 28 for time-to-first cardiovascular death or worsening HF event (HR: 0.63; 95% CI: 0.40-0.97; $P = 0.037$). For the endpoint of total worsening HF events alone, first statistical significance was reached by day 27 (RR: 0.58; 95% CI: 0.35-0.95; $P = 0.031$). Sustained benefits on the primary endpoint were observed at days 30, 90, 180, and at 1 year, 2 years, and at final follow-up (Figure 1B).

DISCUSSION

In this prespecified analysis of the FINEARTS-HF trial, first statistical significance for the primary endpoint was observed within 1 month of therapeutic initiation, a benefit that was sustained until final follow-up. Rapid statistical significance on similar timelines have been also demonstrated with steroidal MRAs when tested in adjacent populations of HF with reduced ejection fraction (first statistical significance on day 26).[5] This early time course of benefit is also well aligned with estimates from trials of sodium-glucose cotransporter 2 inhibitors (first statistical significance on days 13 and 18), the only other therapy with definitive evidence of favorable efficacy in HF with mildly reduced or preserved ejection fraction.[6,7]

Mechanistically, finerenone may induce early natriuresis, reduce generation of reactive oxygen species, improve endothelial dysfunction, modulate inflammatory processes, and lower blood pressure, which might collectively explain its early clinical benefits. The heightened early burden of worsening HF events may be most sensitive to shifts in sodium and water that appear to be favorably influenced even after initial dosing of finerenone.[1] These data suggest that decongestive mechanisms likely play a key role in the early benefits observed with finerenone, regardless of effects that may manifest later.

The key limitation of this analysis is the assumption that first statistical significance is commensurate with the first clinical benefits afforded by finerenone, because statistical significance is influenced by not only the magnitude of treatment effect but also the size of the population studied and number of clinical events accrued in the early time frame. Although the exact onset of clinical benefit of a therapy may be difficult to ascertain in trials examining discrete events, first statistical significance provides a conservative approximation of this time line. Near immediate separation of the event curves suggest potential favorable clinical benefits may indeed manifest even earlier after starting the therapy, but events were too few with wide confidence limits at these very early time points to show statistical significance.

In the FINEARTS-HF trial, finerenone achieved early benefits that were clinically meaningful and statistically significant by 1 month of its initiation. In concert with data from steroidal MRAs in patients with HF with reduced ejection fraction, these data suggest that MRAs induce a rapid decongestive and hemodynamic response that may account for its early benefit. Whereas HF with mildly reduced or preserved ejection fraction has conventionally been managed with a lesser sense of urgency compared with HF with reduced ejection fraction, these data underscore the early modifiable risks faced by this population and support the rapid implementation of finerenone alongside other standard of care therapies such as the sodium-glucose cotransporter 2 inhibitors.

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FINEARTS-HF was funded by Bayer AG. Dr Vaduganathan has received research grant support, served on Advisory Boards, or had speaker engagements with American Regent, Amgen, AstraZeneca, Bayer AG, Baxter Healthcare, Bristol Myers Squibb, Boehringer Ingelheim, Chiesi, Cytokinetics, Fresenius Medical Care, Idorsia Pharmaceuticals, Lexicon Pharmaceuticals, Merck, Milestone Pharmaceuticals, Novartis, Novo Nordisk, Pharmacosmos, Relypsa, Roche Diagnostics, Sanofi, and Tricog Health; and has participated on Clinical Trial Committees for studies sponsored by AstraZeneca, Galmed, Novartis, Bayer AG, Occlutech, and Impulse Dynamics. Dr Claggett has received personal consulting fees from Alnylam, Bristol Myers Squibb, Cardior, Cardurion, Corvia, CVRx, Eli Lilly, Intellia, and Rocket; and has served on a Data Safety Monitoring Board for Novo Nordisk. Dr Desai has received institutional research grants (to Brigham and Women's Hospital) from Abbott, Alnylam, AstraZeneca, Bayer, Novartis, and Pfizer; and has received personal consulting fees from Abbott, Alnylam, AstraZeneca, Bayer, Biofourmis, Boston Scientific, Medpace, Medtronic, Merck, Novartis, Parexel, Porter Health, Regeneron, River2Renal, Roche, Veristat, Verily, and Zydus. Dr Jhund has received speaker fees from AstraZeneca, Novartis, Alkem Laboratories, ProAdWise Communications, and Sun Pharmaceuticals; has received Advisory Board fees from AstraZeneca, Boehringer Ingelheim, and Novartis; has received research funding from AstraZeneca, Boehringer Ingelheim, Analog Devices Inc, and Roche Diagnostics; his employer, the University of Glasgow, has been remunerated for clinical trial work from AstraZeneca, Bayer AG, Novartis, and Novo Nordisk; and he has served as director of GCTP Ltd. Dr Lam has received research support from Novo Nordisk and Roche Diagnostics; has received consulting fees from Alleviant Medical, Allysta Pharmaceuticals, AnaCardio AB, Applied Therapeutics, AstraZeneca, Bayer, Biopeutics, Boehringer Ingelheim, Boston Scientific, Bristol Myers Squibb, CardioRenal, CPC Clinical

Research, Eli Lilly, Impulse Dynamics, Intellia Therapeutics, Ionis Pharmaceutical, Janssen Research and Development LLC, Medscape/WebMD Global LLC, Merck, Novartis, Novo Nordisk, ProSciento Inc, Quidel Corporation, Radcliffe Group Ltd, Recardio Inc, ReCor Medical, Roche Diagnostics, Sanofi, Siemens Healthcare Diagnostics, and Us2.ai; and is a cofounder and nonexecutive director of Us2.ai. Dr Senni has served on the Advisory Boards of and has received consulting fees or honoraria from Novartis, Abbott, Merck, Merck Sharp & Dohme, Vifor, AstraZeneca, Cardurion, Novo Nordisk, Bayer, and Boehringer Ingelheim. Dr Shah has received research grants from the National Institutes of Health (U54 HL160273, X01 HL169712, R01 HL140731, R01 HL149423), the American Heart Association (24SFRNPCN1291224), AstraZeneca, Corvia, and Pfizer; and has received consulting fees from Abbott, Alleviant, AstraZeneca, Amgen, Aria CV, Axon Therapies, Bayer, Boehringer Ingelheim, Boston Scientific, Bristol Myers Squibb, Cyclerion, Cytokinetics, Edwards Lifesciences, Eidos, Imara, Impulse Dynamics, Intellia, Ionis, Lilly, Merck, MyoKardia, Novartis, Novo Nordisk, Pfizer, Prothena, Regeneron, Rivus, Sardocor, Shifamed, Tenax, Tenaya, and Ultromics. Dr Voor's employer has received consulting fees and/or research support from Adrenomed, AnaCardio, AstraZeneca, Bayer AG, Bristol Myers Squibb, Boehringer Ingelheim, Corteria, Eli Lilly, Merck, Moderna, Novartis, Novo Nordisk, Roche Diagnostics, and SalubrisBio. Dr Zannad has received personal fees from 89Bio, Abbott, Acceleron, Applied Therapeutics, Bayer, Betagenon, Boehringer, Bristol Myers Squibb, CVRx, Cambrian, Cardior, Cereno Pharmaceutical, CellProthera, CEVA, Inventiva, KBP Biosciences, Merck, Novo Nordisk, Owkin, Otsuka, Roche Diagnostics, NorthSea, and USa2; holds stock options at G3Pharmaceutical; holds equities at Cereno, CardioRenal, and Eshmoun Clinical Research; and is the founder of Cardiovascular Clinical Trialists. Dr Pitt has served as a consultant for Bayer, AstraZeneca, Bristol Myers Squibb, Boehringer Ingelheim, Lexicon, Anacardia, and G3 Pharmaceuticvals; has served as a consultant and received stock options or stocks from Sea Star Medical, Vifor, scPharmaceuticals, SQinnovations, KBP Biosciences, Sarfez, Cereno Scientific, Prointel, and Brainstorm Medical; holds a U.S. Patent (9931412-site specific delivery of Eplerenone to the myocardium); and has a U.S. Patent pending (63/045,783 Histone Modulating agents for the prevention and treatment of organ damage). Dr McMurray has received payments through Glasgow University from work on clinical trials, consulting fees, and grants from Amgen, AstraZeneca, Bayer, Cardurion, Cytokinetics, GlaxoSmithKline, and Novartis; has received personal consultancy fees from Alynylam Pharmaceuticals, Amgen, AnaCardio, AstraZeneca, Bayer, Berlin Cures, Bristol Myers Squibb, Cardurion, Cytokinetics, Ionis Pharmaceuticals, Novartis, Regeneron Pharmaceuticals, River 2 Renal Corp, British Heart Foundation, National Institutes of Health/National Heart, Lung, and Blood Institute, Boehringer Ingelheim, SQ Innovations, and Catalyze Group; has received personal lecture fees from Abbott, Alkem Metabolics, AstraZeneca, Blue Ocean Scientific Solutions Ltd, Boehringer Ingelheim, Canadian Medical and Surgical Knowledge, Emcure Pharmaceuticals Ltd, Eris Lifesciences, European Academy of CME, Hikma Pharmaceuticals, Imagica Health, Intas Pharmaceuticals, J.B. Chemicals and Pharmaceuticals Ltd, Lupin Pharmaceuticals, Medscape/Heart.Org, ProAdWise Communications, Radcliffe Cardiology, Sun Pharmaceuticals, The Corpus, Translation Research Group, and Translational Medicine Academy; has served on Data Safety Monitoring Board WIRB-Copernicus Group Clinical Inc; and is a director of Global Clinical Trial Partners Ltd. Dr Solomon has received research grants from Alexion, Alnylam, AstraZeneca, Bellerophon, Bayer, Bristol Myers Squibb, Boston Scientific, Cytokinetics, Edgewise, Eidos, Gossamer, GlaxoSmithKline, Ionis, Lilly, MyoKardia, National Institutes of Health/National Heart, Lung, and Blood Institute, Novartis, Novo Nordisk, Respicardia, Sanofi Pasteur, Theracos, and Us2.ai; and has consulted for Abbott, Action, Akros, Alexion, Alnylam, Amgen, Arena, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Cardior, Cardurion, Corvia, Cytokinetics, Daiichi-Sankyo, GlaxoSmithKline, Lilly, Merck, MyoKardia, Novartis, Roche, Theracos, Quantum Genomics, Janssen, Cardiac Dimensions, Tenaya, Sanofi-Pasteur, DiNAQOR, Tremeau, CellProthera, Moderna, American Regent, Sarepta, Lexicon, AnaCardio, Akros, and Valo.

ADDRESS FOR CORRESPONDENCE: Dr Scott D. Solomon, Brigham and Women's Hospital, Harvard Medical School, 75 Francis Street, Boston, Massachusetts 02115, USA. E-mail: ssolomon@rics.bwh.harvard.edu.

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