VITALITY -HFpEF

NCT03547583

Vericiguat in Heart Failure with Preserved Ejection Fraction: The VITALITY-HFpEF Trial

Trial to eValuate the efflcacy and safeTy of the orAL sGC stImulator vericiguaT to improve phYsical functioning in activities of daily living in patients with HFpEF

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on behalf of the VITALITY-HFpEF Study Group

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Disclosures

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Dr. Armstrong reports research grants from Merck & Co, Inc, Bayer AG, and consulting fees from Merck & Co, Inc, Bayer AG, AstraZeneca, and Novartis.

- Available online: thecvc.ca

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sGC and Physical Function in HFpEF

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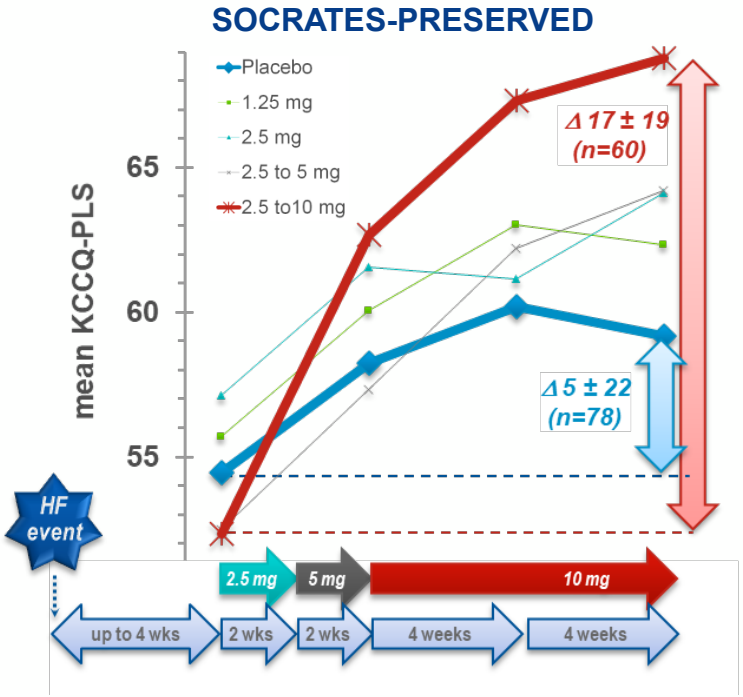
- Patients with HFpEF have substantially reduced functional capacity and quality of life[1]
- No treatment exists to address this major unmet need[2]
- Physiologic stimulation of sGC by NO is disrupted in HFpEF due to comorbidity-related inflammation[3]
- Soluble guanylate cyclase (sGC) has a unique mechanism enhancing heart, vessel, muscle, and renal function

- **SOCRATES-PRESERVED suggested improvement in KCCQ-PLS with vericiguat in HFpEF**



[1] Butler et al. *Circ Heart Fail*. 2016 Nov;9(11)
[2] Yancy CW et al. *J Am Coll Cardiol.* 2017 Aug 8;70(6):776-803
[3] Shah S et al. *Circulation.* 2016;134:73-90

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D mean ± standard deviation
Full analysis set excluding subjects with incorrectly assigned doses
Filippatos et al. Eur J Heart Fail. 2017 Jun;19(6):782-791

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Study Design

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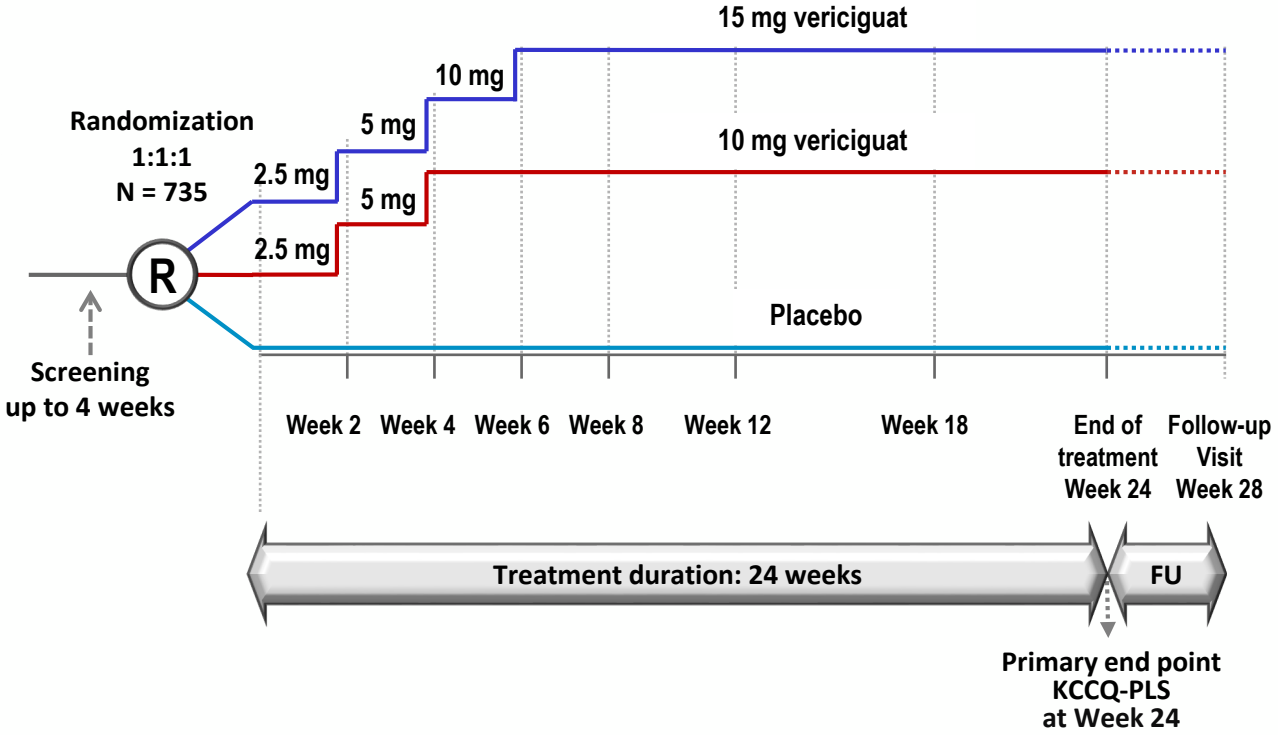
Previous diagnosis of chronic HF
HF event within 6mos
Elevated NT-proBNP/BNP
EF ≥45%
And
LVH and/or LAE
NYHA class II/III



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VITALITY-HFpEF Patient Population

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- HF decompensation <6 months:
  defined as HF hospitalization **or** IV diuretic for HF
- **Natriuretic peptide criteria:**
  - in sinus rhythm: NT-proBNP ≥300 or BNP ≥100 pg/mL
  - in atrial fibrillation: NT-proBNP ≥600 or BNP ≥200 pg/mL
- **Exclusions:** Concurrent or anticipated use of nitrates or PD-type 5 inhibitors, and/or prior diagnosis of LVEF <40%

VITALITY-HFpEF Study Endpoints

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Primary endpoint:

- Change from baseline to week 24 in physical limitations measured by the KCCQ PLS

Secondary endpoint:

- Change from baseline to week 24 in the 6 MWT

Safety:

- Symptomatic hypotension and syncope were adverse events of special interest

VITALITY-HFpEF Statistical Analysis

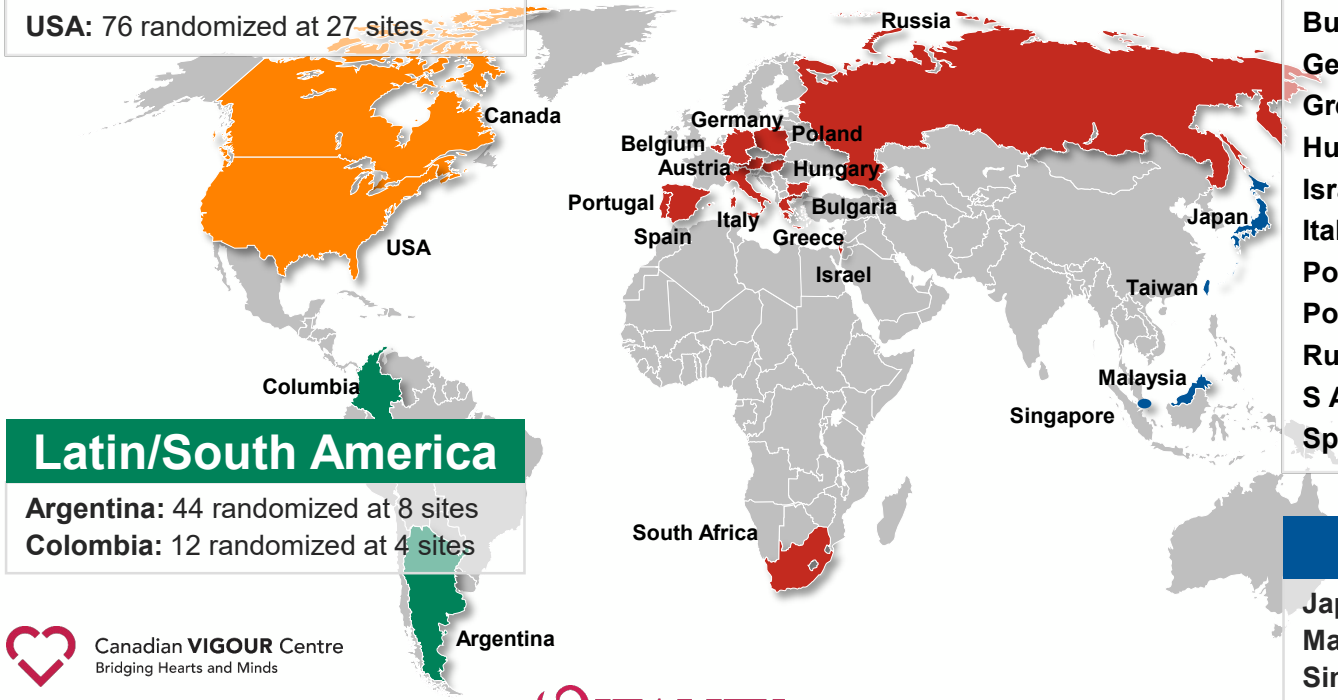
Primary analysis:

- Repeated-measures mixed model: include all assessments post baseline; KCCQ-PLS contrast at 24 weeks as test point for the primary analysis of difference in least squares (LS) means at week 24.(Type I error control)
- Power 80% for rejecting either of the two primary hypotheses (vericiguat 15 mg vs. plac and 10 mg vs. plac arms); *assuming 5 point KCCQ-PLS difference between each comparison (SD=21 points).*
- Overall 2-sided α 0.05. Type I error protected using graphical method (Maurer and Bretz 2013).

Enrollment by Region and Country

North America

Canada: 23 randomized at 7 sites
USA: 76 randomized at 27 sites



Latin/South America

Argentina: 44 randomized at 8 sites
Colombia: 12 randomized at 4 sites

Europe/Africa

Austria: 35 randomized at 7 sites
Belgium: 11 randomized at 5 sites
Bulgaria: 96 randomized at 8 sites
Germany: 19 randomized at 6 sites
Greece: 48 randomized at 6 sites
Hungary: 43 randomized at 6 sites
Israel: 61 randomized at 10 sites
Italy: 44 randomized at 9 sites
Poland: 70 randomized at 8 sites
Portugal: 25 randomized at 7 sites
Russia: 63 randomized at 6 sites
S Africa: 18 randomized at 6 sites
Spain: 29 randomized at 9 sites

Asia

Japan: 41 randomized at 21 sites
Malaysia: 5 randomized at 2 sites
Singapore: 5 randomized at 2 sites
Taiwan: 21 randomized at 4 sites

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Patient Enrollment

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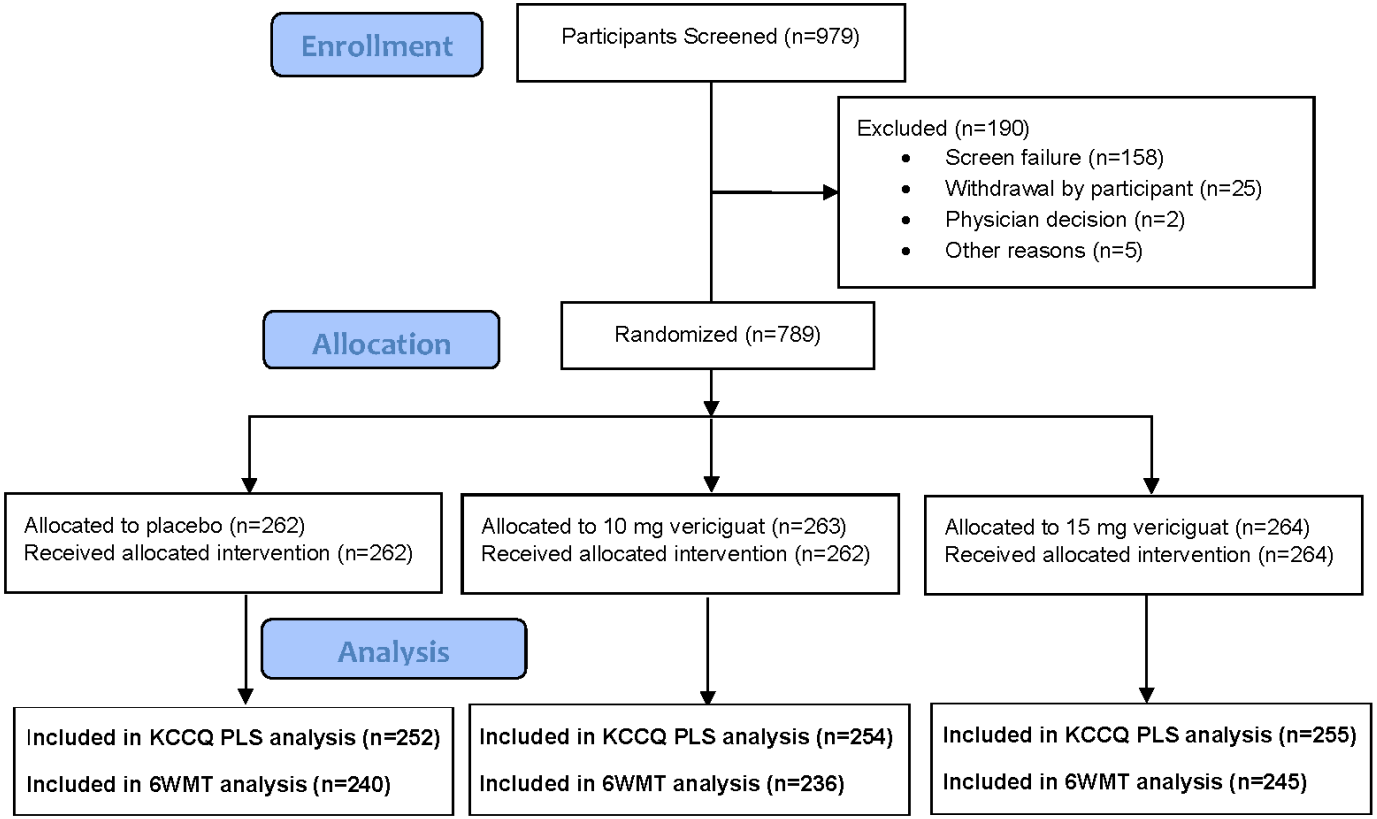

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Selected Baseline Characteristics

Variable	Placebo (N=262)	Vericiguat 10 mg (N=263)	Vericiguat 15 mg (N=264)
Age, mean (SD), yrs	72.8 (9.4)	72.2 (9.7)	73.1 (9.1)
Female sex, no. (%)	121 (46.2%)	124 (47.1%)	140 (53.0%)
Coronary artery disease	127 (48.5%)	115 (43.7%)	120 (45.5%)
NYHA class III, no. (%)	106 (40.5%)	109 (41.4%)	112 (42.4%)
SBP, mean (SD), mm Hg	129.0 (12.2)	129.8 (12.6)	129.3 (13.0)
Heart rate, mean (SD), beats/min	70.1 (10.6)	70.9 (11.0)	70.3 (10.5)
Atrial fibrillation	86 (32.8%)	94 (35.7%)	96 (36.4%)
eGFR, mean (SD), mL/min/1.73m^2	56.9 (20.0)	62.4 (20.6)	59.1 (21.2)
NT-proBNP, median (IQ), pg/m	1644.2 (795.8, 3161.2)	1339.1 (718.7, 3042.5)	1364.5 (555.1, 2826.5)
LVEF at baseline, mean (SD)	56.3 (7.9)	55.8 (8.3)	56.8 (7.9)

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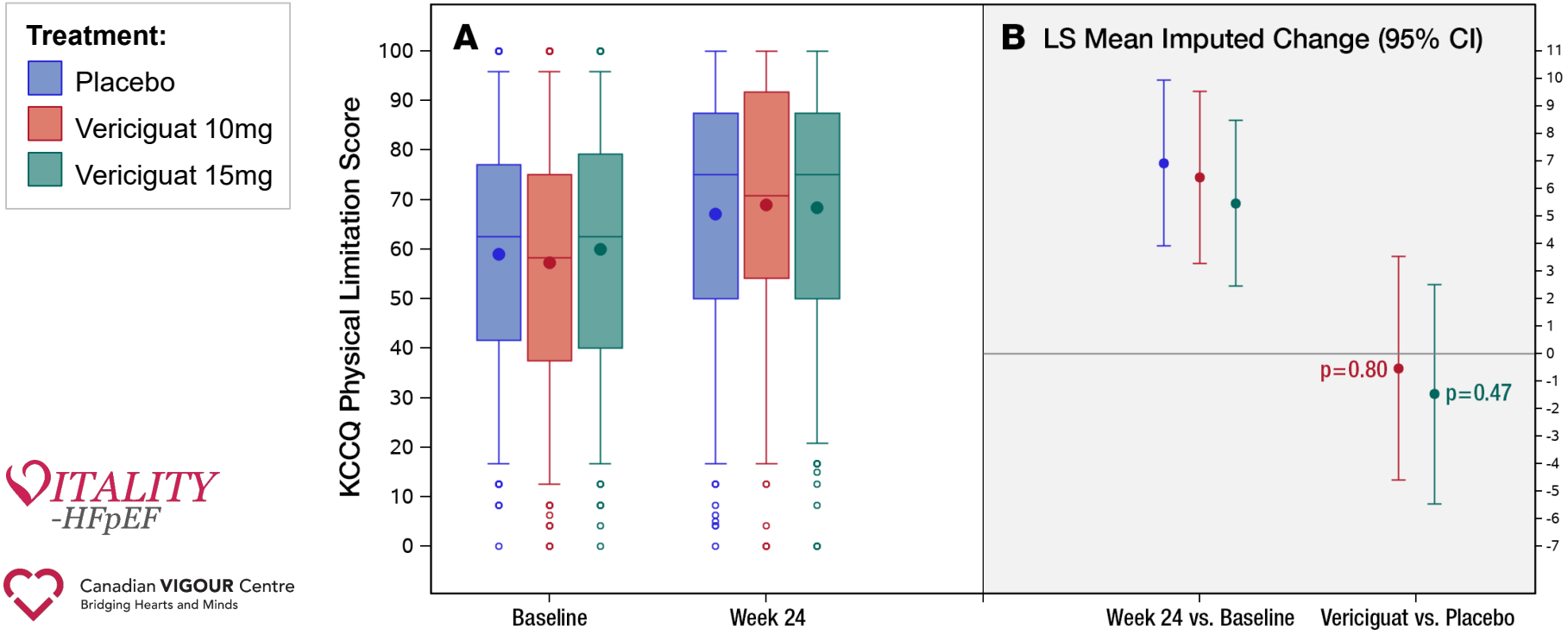
Primary Endpoint: *KCCQ PLS Scores*



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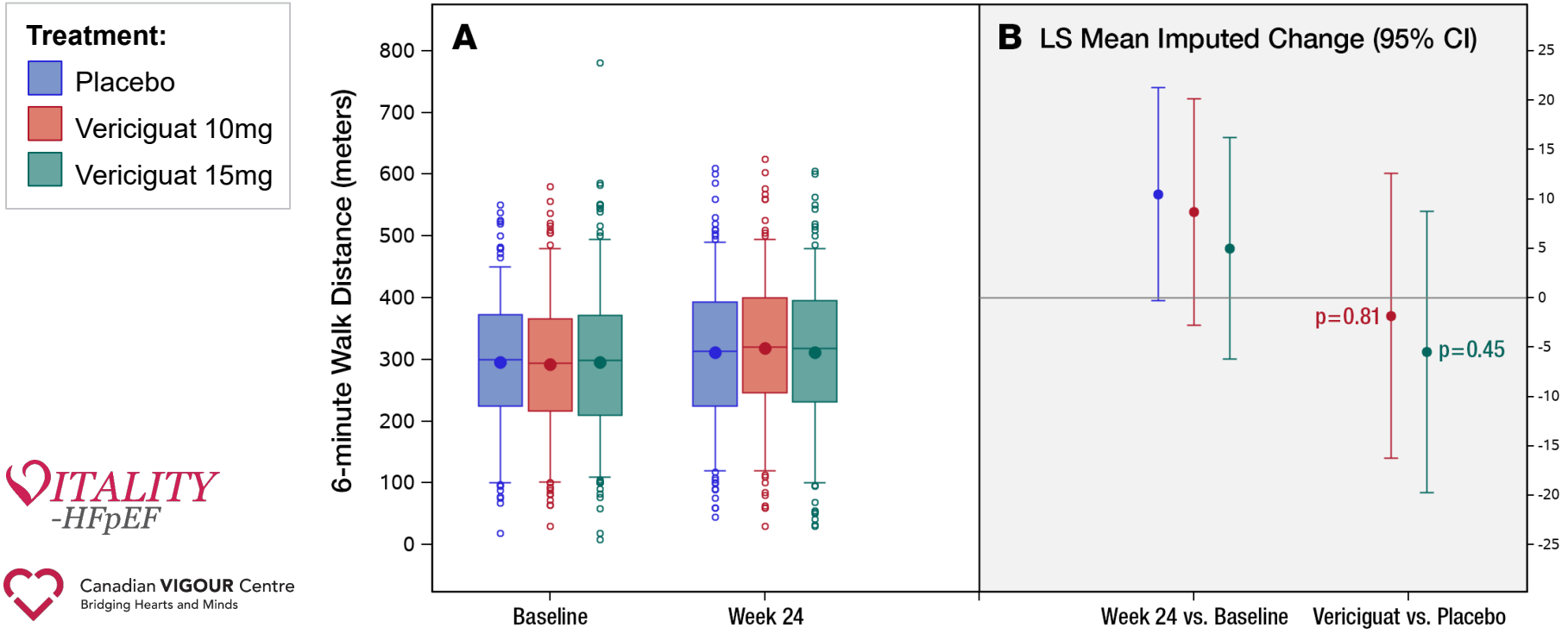
Secondary Endpoint: *6-Minute Walking Distances*



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Summary Treatment—
Emergent Adverse Events

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Variable	Placebo (N=262)	Vericiguat 10 mg (N=262)	Vericiguat 15 mg (N=264)
Any AE	172 (65.6%)	163 (62.2%)	172 (65.2%)
Any study drug-related AE	24 (9.2%)	38 (14.5%)	42 (15.9%)
Any AE leading to discontinuation of study drug	7 (2.7%)	9 (3.4%)	12 (4.5%)
AEs of special interest			
Symptomatic hypotension	9 (3.4%)	11 (4.2%)	17 (6.4%)
Syncope	1 (0.4%	2 (0.8%)	4 (1.5%)
Cardiovascular death	4 (1.5%)	12 (4.6%)	8 (3.0%)
All-cause death	7 (2.7%)	15 (5.7%)	10 (3.8%)

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Data presented as number (%) of patients with treatment-emergent adverse events.

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Summary

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- Vericiguat in target doses of 10 and 15 mg did not improve the primary outcome of KCCQ PLS nor the secondary outcome of 6-minute walking distance in a typical HFpEF population.
- Tendency for more symptomatic hypotension& syncope with both 10 and 15 mg doses suggests a pharmacodynamically active dose studied.
- Although there were more CV deaths in the vericiguat groups, the limited duration of follow up and numbers are too small for definitive conclusions.

Conclusion

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- In the VITALITY-HFpEF trial, vericiguat (10 or 15 mg) compared with placebo did not improve KCCQ PLS scores or 6MWD.
- SOCRATES PRESERVED findings were not confirmed in larger population studied with two doses for a longer time
- VITALITY aligned with prior studies of the NO-sGC-cGMP pathway that did not improve HFpEF
- Further studies are needed to identify effective interventions to improve outcomes in patients with HFpEF

Trial Organization

STEERING COMMITTEE

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Robert Blaustein.
Justin Ezekowitz
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Adriaan Voors
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Padma Kaul
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Josephine Norquist
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Selected Baseline Characteristics (continued)

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Variable	Placebo (N=262)	Vericiguat 10 mg (N=263)	Vericiguat 15 mg (N=264)
Anemia	61 (23.3%)	50 (19.0%)	58 (22.0%)
COPD	51 (19.5%)	46 (17.5%)	57 (21.6%)
CKD	116 (44.3%)	92 (35.0%)	110 (41.7%)
Diabetes mellitus	123 (46.9%)	115 (43.7%)	120 (45.5%)
Arterial hypertension	243 (92.7%)	243 (92.4%)	243 (92.0%)
Weight, mean (SD), kg	84.3 (18.8)	83.3 (19.2)	83.9 (19.5)
QHF event before discharge HFH, no. (%)	7 (2.7%)	11 (4.2%)	12 (4.5%)
QHF event after discharge HFH, no. (%)	173 (66.0%)	184 (70.0%)	162 (61.4%)
QHF event IV diuretic treatment no HFH, no. (%)	82 (31.3%)	68 (25.9%)	90 (34.1%)