Serelaxin, A Novel Treatment for Acute Heart Failure- The RELAX-AHF Trial

Prof. John R. Teerlink, MD, FAHA
University of California, San Francisco
and San Francisco VA Medical Center

Prof. Marco Metra, MD
University of Brescia, Brescia, Italy

on behalf of the RELAX-AHF Executive and Steering Committees, Investigators & Patients

Pregnancy & the Heart

PARAMETER	PREGNANCY
Cardiac Output (L/min)	20% Increase
Systemic Vascular Resistance (dyn.s.cm^2)	30% Decrease
Global Arterial Compliance (mL/mm Hg)	30% Increase
Renal Blood Flow (mL/min/ 1.73m^2)	50-85% Increase
Creatinine Clearance (mL/ min/1.73m^2)	40-65% Increase

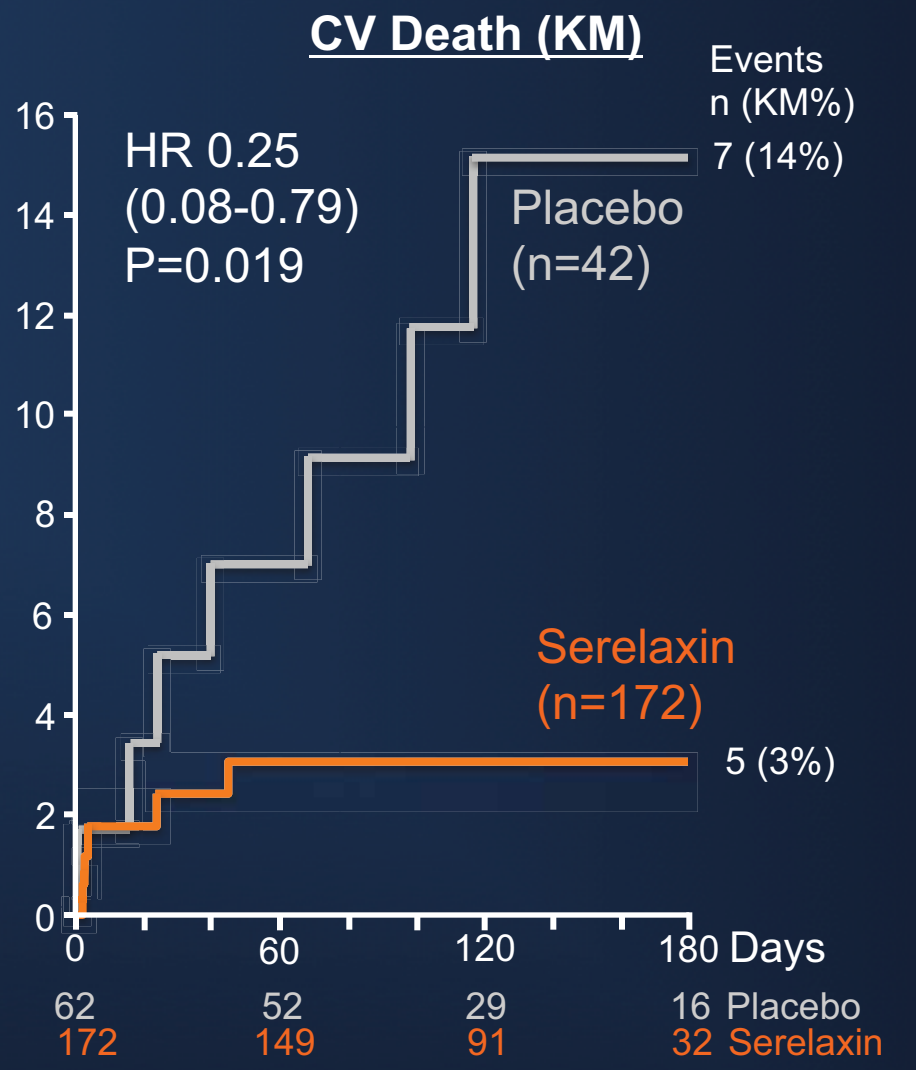
- Relaxin has been shown to mediate these changes, as well as to have anti-ischemic, anti-inflammatory, anti-fibrotic effects.
- Relaxin is elevated through 9 months of pregnancy and mediates physiologic hemodynamic adjustments to growing baby
- Pharmacologic use of serelaxin may produce these beneficial effects in acute heart failure

Baylis, C. *Am J Kid Dis* 1999; Schrier, RW, et al. *Am J Kid Dis* 1987; Jeyebalan, A, et al. *Adv Exp Med Biol* 2007; Teichman SL et al. *Curr Heart Fail Rep* 2010;7:75–82.
Helal I, et al. *Nature Reviews* 2012;293-300.

Pre-RELAX-AHF

Teerlink JR, et al. *Lancet* 2009;373:1429-39.

- 234 patient, dose finding Phase II study
- Optimal dose across multiple clinical outcome domains was 30mcg/kg/d
- Serelaxin had trends to:
  - Improved dyspnea relief
  - Decreased congestion
  - Reduced diuretic use
  - Less worsening of heart failure
  - Shorter length of stay
  - Reduced days alive out of hospital
  - Improved cardiovascular and all-cause survival
- No significant adverse events
- No hypotension SAEs; Hypotension AEs similar to placebo



Objectives and Hypothesis

- Based upon the hypothesis-generating results of Pre-RELAX-AHF, the RELAX-AHF trial was designed to test the efficacy and safety of serelaxin in patients with acute heart failure (AHF).
- We hypothesized that serelaxin (30 mcg/kg/d iv) would improve dyspnea to a greater extent than placebo by one or both measures at 24 hours (Likert) and/or 5 days (VAS AUC), and improve other clinical outcomes.

Inclusion and Exclusion Criteria

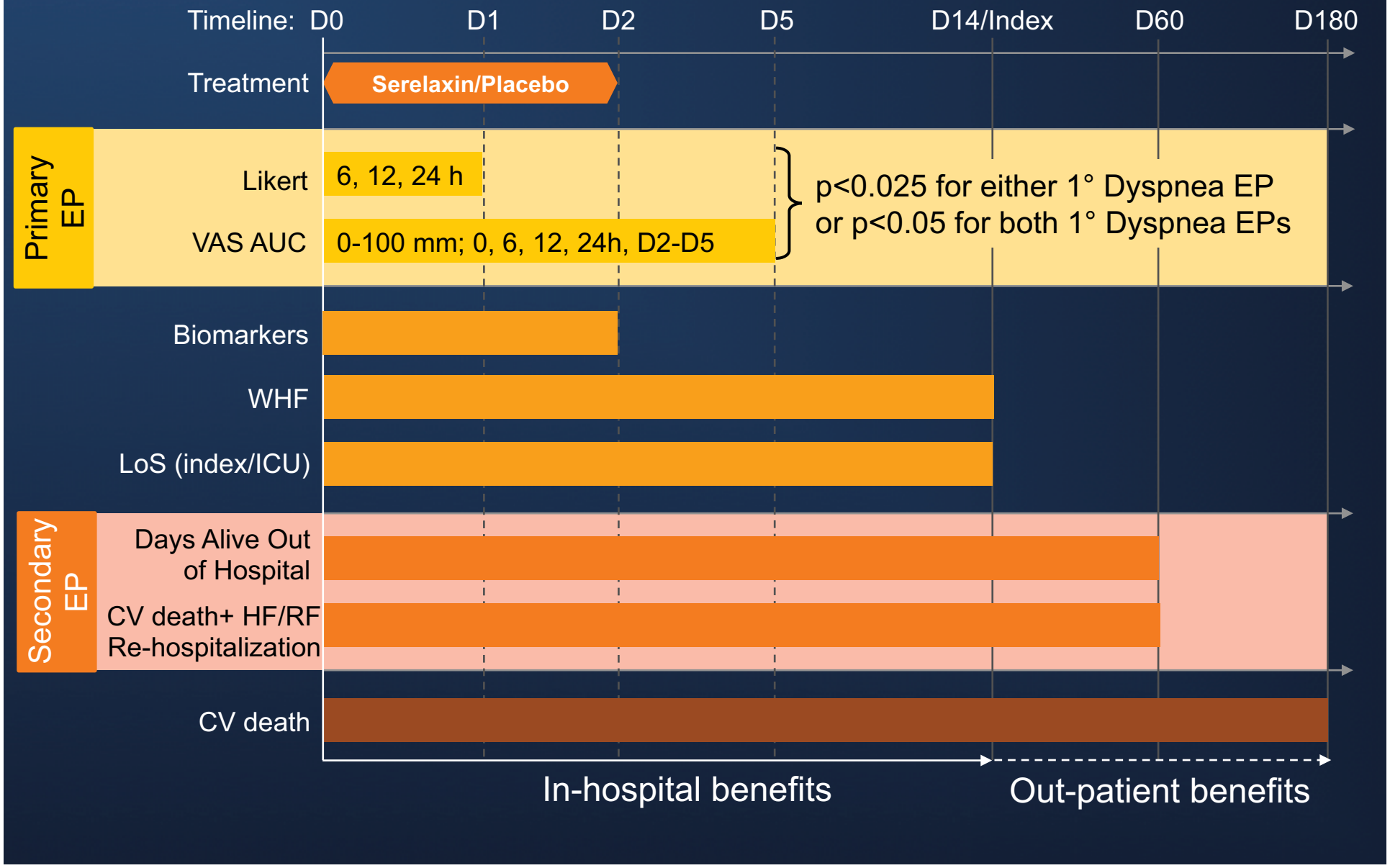
Key Inclusion Criteria

- Hospitalized for AHF
  - Dyspnea at rest or with minimal exertion
  - Pulmonary congestion on chest radiograph
  - BNP ≥ 350 pg/mL or NT-pro-BNP ≥ 1400 pg/mL
- Received ≥40 mg IV furosemide (or equivalent) at any time between admission to emergency services (either ambulance or hospital, including the ED) and the start of screening for the study
- Systolic blood pressure > 125 mmHg
- Impaired renal function on admission (sMDRD eGFR 30-75 mL/min/1·73 m^2)
- Randomised within 16 hours from presentation
- Age ≥ 18 years of age
- Body weight < 160 kg

Key Exclusion Criteria

- Current or planned treatment with any IV therapies [i.e. other vasodilators, (nesiritide), positive inotropic agents and vasopressors] or mechanical circulatory, renal, or ventilatory support, with the exception of IV furosemide (or equivalent), or of IV nitrates if patient has screening SBP >150 mmHg
- AHF and/or dyspnea from arrhythmias or non-cardiac causes, such as lung disease, anemia, or severe obesity
- Infection or sepsis requiring IV antibiotics
- Pregnant or breast-feeding
- Stroke within 60d; ACS within 45d; major surgery within 30d
- Presence of acute myocarditis, significant valvular heart disease, hypertrophic/ restrictive/ constrictive cardiomyopathy

Key Efficacy Measures



RELAX-AHF

Patient population (1)

Parameter		Placebo (N=580)	Serelaxin (N=581)
Age (years)	Mean	72.5	71.6
Systolic BP at baseline (mmHg)	Mean	142.1	142.2
Heart Rate at Baseline (bpm)	Mean	80.4	78.9
Respiratory Rate at baseline (breaths/ min)	Mean	22.0	21.8
HF Hospitalization (in the past year)	%	31.2	37.2*
Most Recent Ejection Fraction	Mean	38.7	38.6
< 40%	%	54.9	54.7
NYHA (1 month prior to admission)	%		
III	%	46.7	43.7
IV	%	17.0	14.4
Medical History			
Hypertension	%	87.9	85.4
Hyperlipidemia	%	54.0	52.3
Stroke or Other Cerebrovascular event	%	14.5	12.6
Atrial fibrillation/ atrial flutter at presentation	%	42.4	40.1
Diabetes Mellitus	%	46.9	48.0

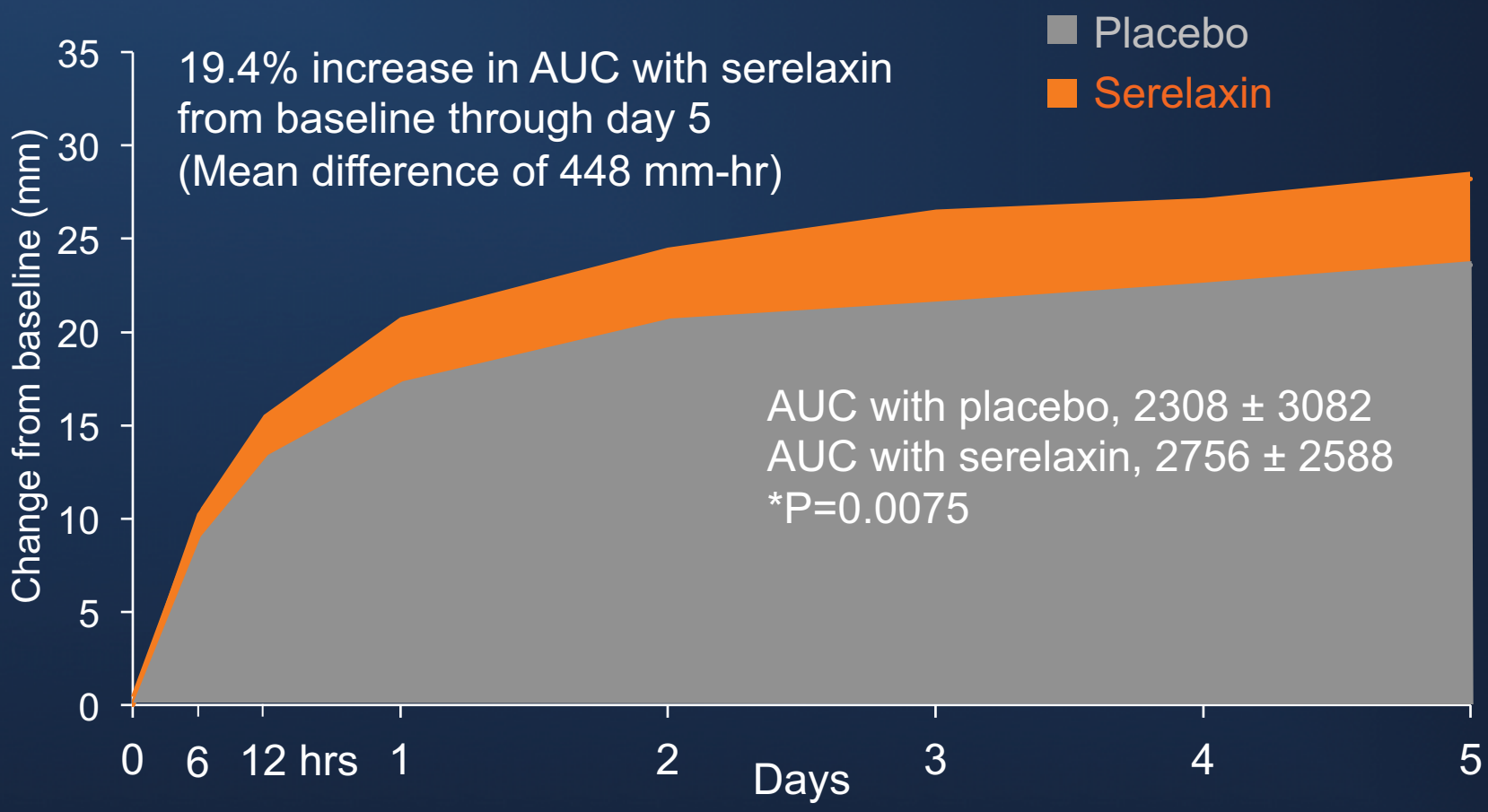
Patient population (2)

Parameter (n' placebo/n' serelaxin)		Placebo (N=580)	Serelaxin (N=581)
Concomitant Heart Failure Meds at Baseline			
ACE inhibitors	%	55.2	53.9
ARB	%	16.7	15.1
Beta-blocker	%	70.2	66.6
Aldosterone antagonist	%	29.8	33.2
Digoxin	%	18.6	20.7
Time from present. to random. (hr)	Mean	7.9	7.8
Duration of study drug administration (hr)	Mean	43.8	41.2
IV nitrates at randomisation	%	7.2	6.7
NT-proBNP (mg/L)**	Geometric Mean	5003	5125
Troponin T (pg/ml)**	Geometric Mean	0.036	0.034
eGFR (MDRD; mL/kg/1.73m^2)	Mean	53.3	53.7

** Core lab values

RELAX-AHF

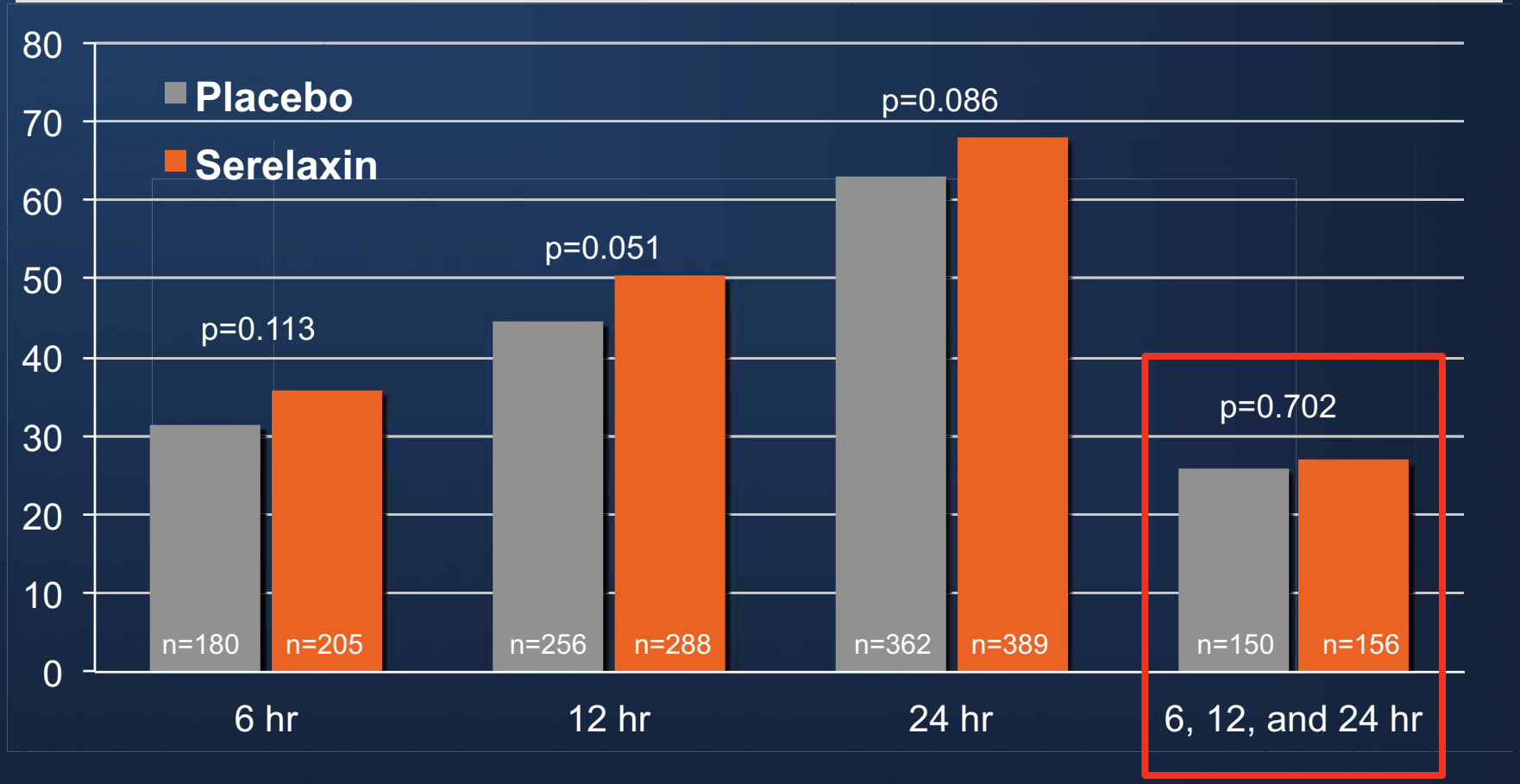
1° Endpoint: Dyspnea Relief (VAS AUC)



RELAX-AHF

1° Endpoint: Dyspnea Relief (Likert)

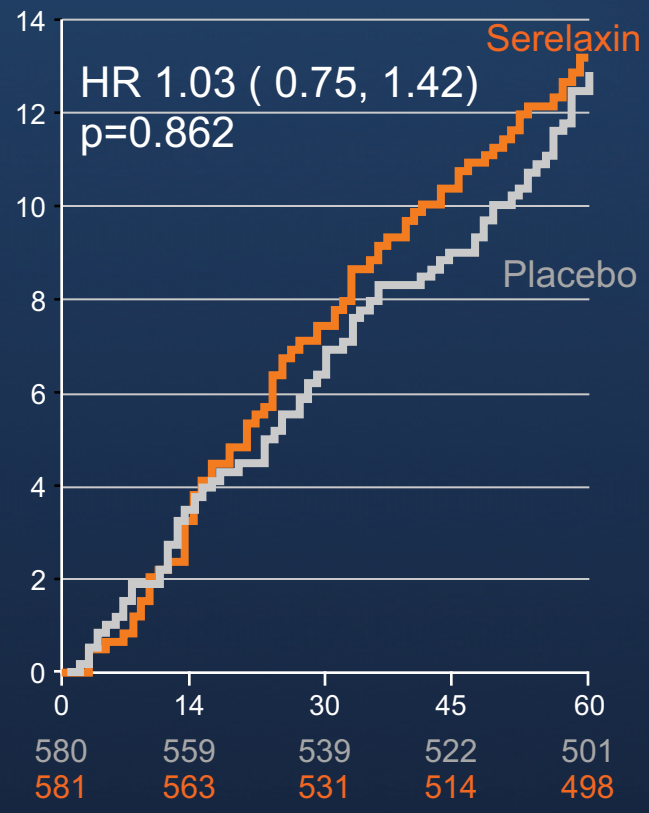
Proportion of subjects with moderately or markedly better dyspnea by Likert by time point



p value by Chi-square test

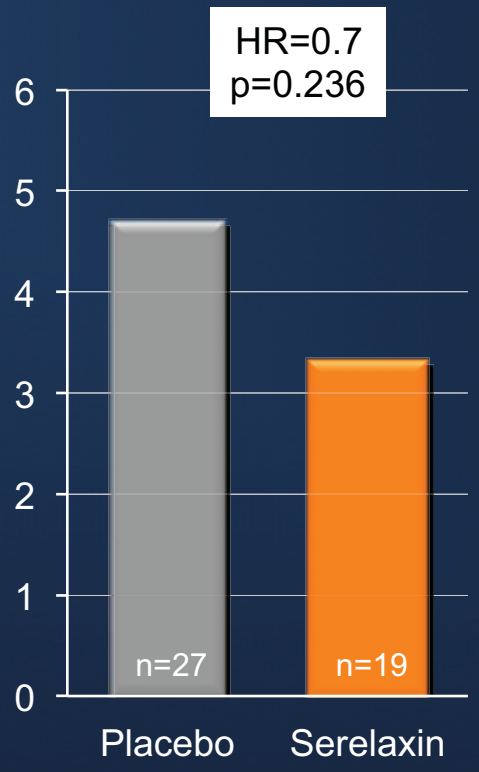
2° Endpoint: CV Death or HF/RF Re-hospitalization through Day 60

K-M estimate for time to first event (%)

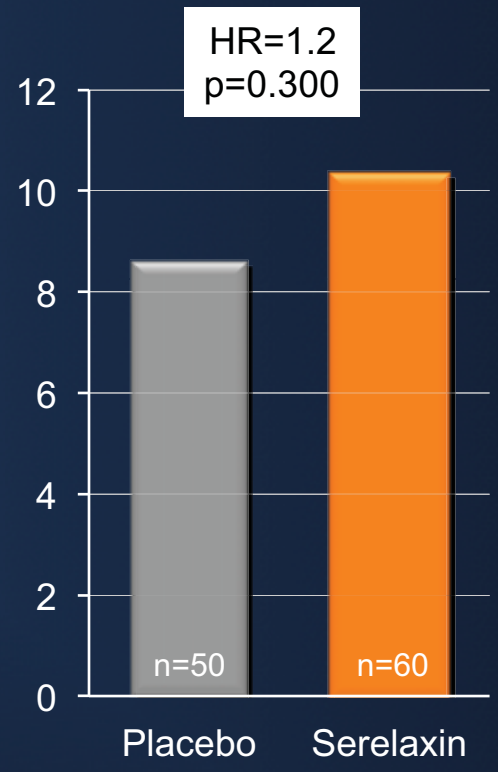


* p value by log rank test
**HR estimate by Cox model

Composite event components (%)



CV death: % subjects



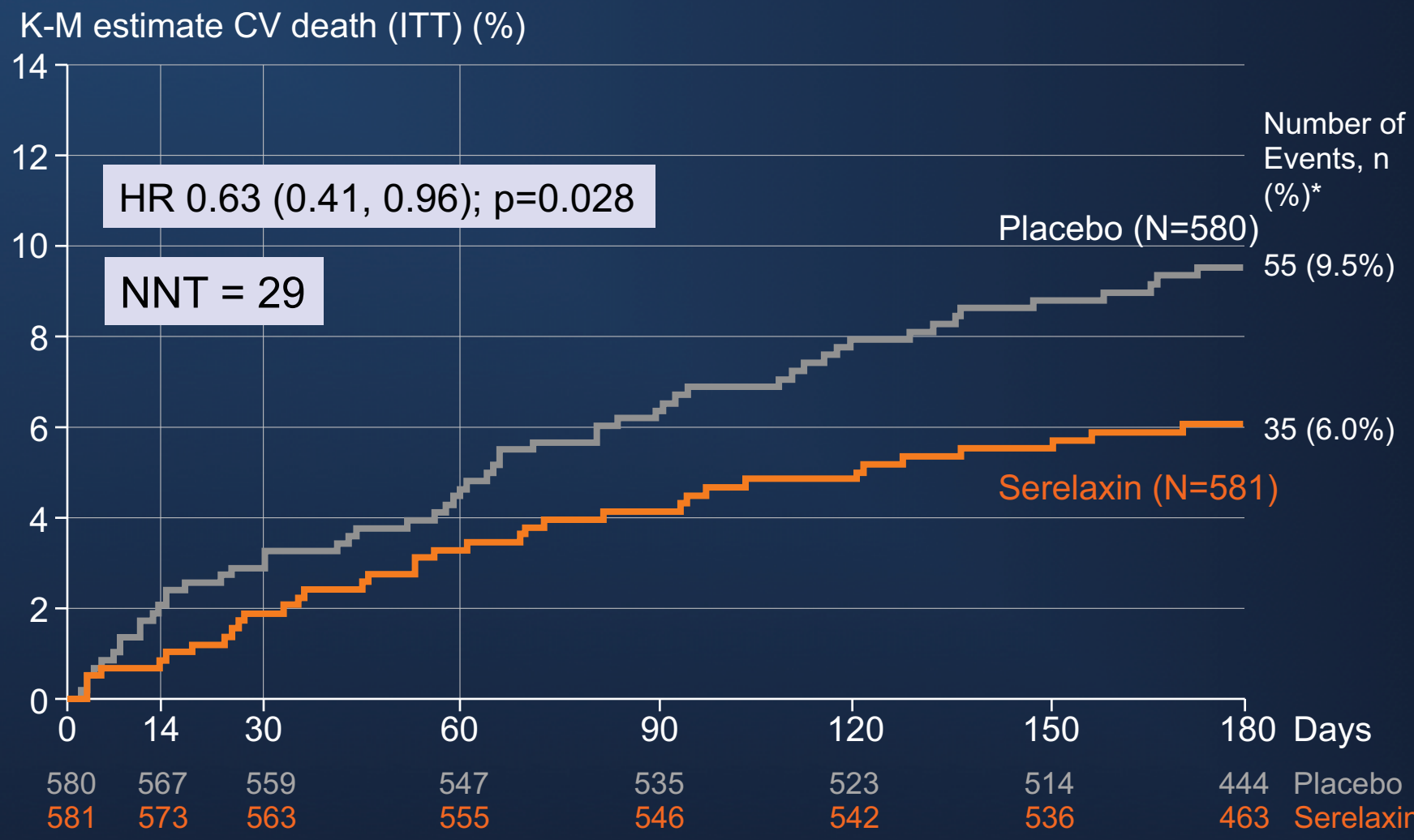
HF/RF re-hospitalization: % subjects

2° Endpoint: Days Alive and Out of Hospital through Day 60

Days Alive Out of Hospital = total follow-up time (D60) - days in hospital or dead
*p value by 2-sided Wilcoxon rank sum test

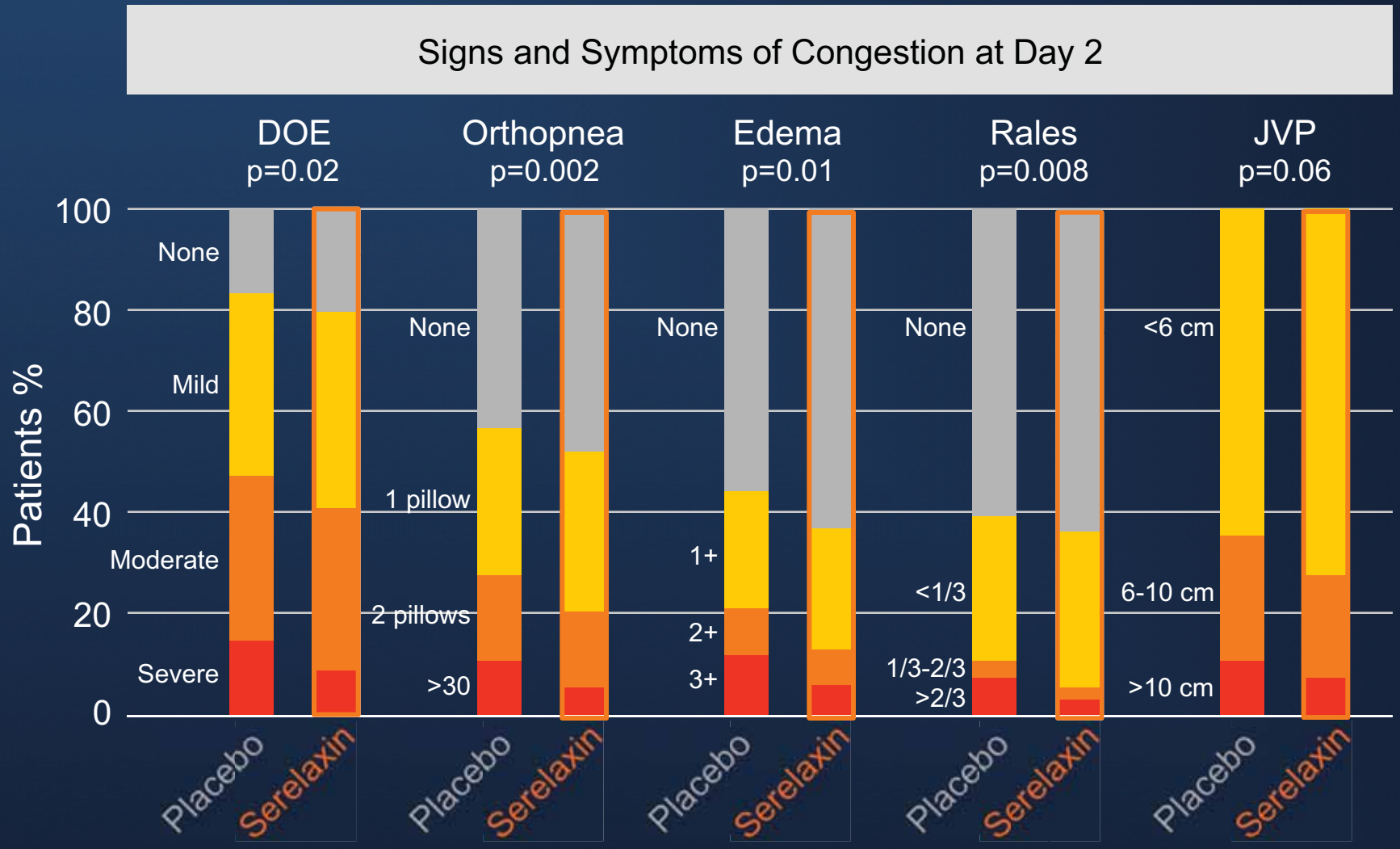
RELAX-AHF

CV Death through Day 180



RELAX-AHF

Signs and Symptoms of Congestion

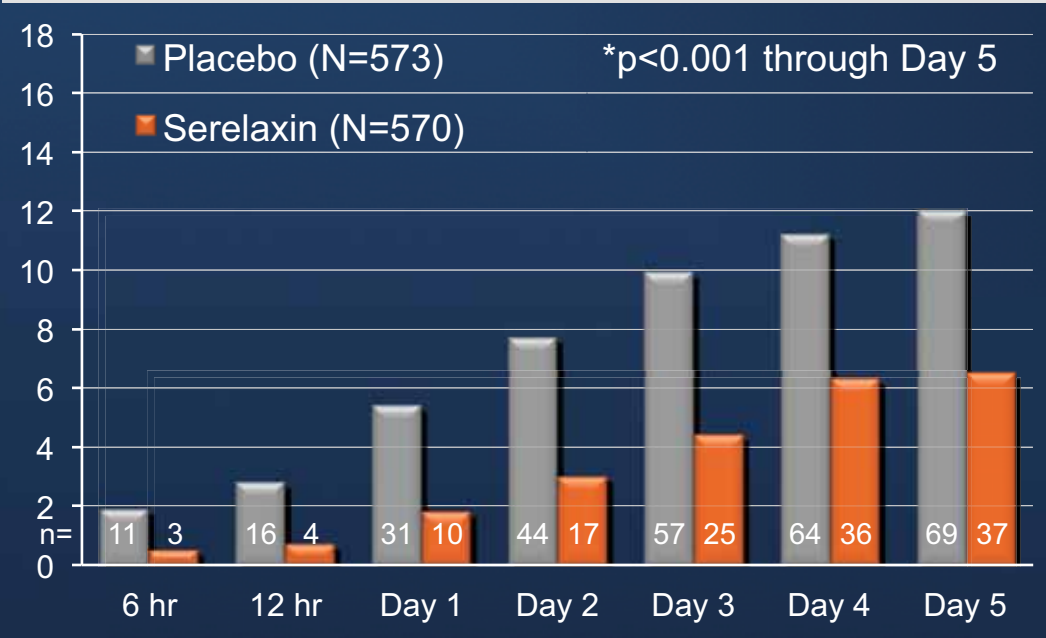


p value by 2-sided Wilcoxon rank sum test of change from baseline

RELAX-AHF

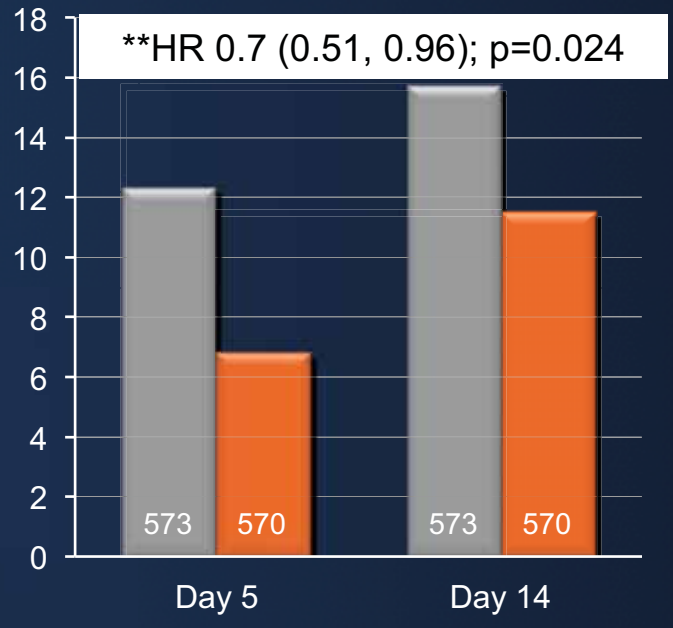
Worsening of Heart Failure

Cumulative proportion of worsening heart failure to Day 5 (%)



(Numbers of subjects with WHF shown for each time point)

Kaplan-Meier estimate D14 for time to WHF (%)

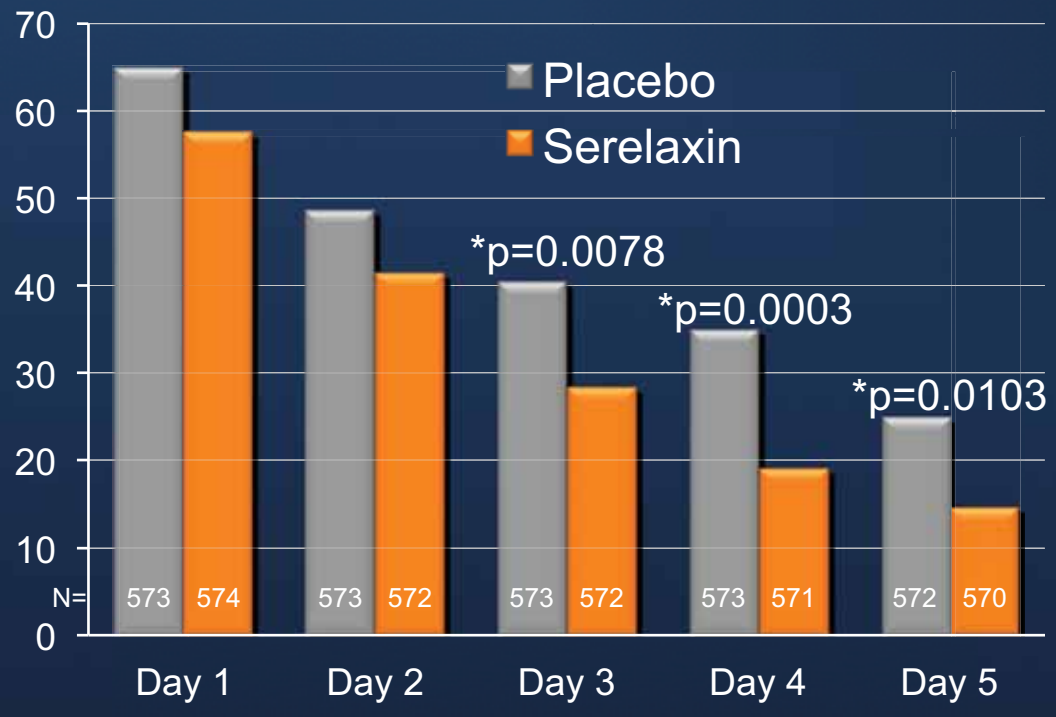


Worsening Heart Failure (WHF) was defined as worsening signs and/or symptoms of HF that required an intensification of IV therapy for heart failure or mechanical ventilatory or circulatory support.

*p value by Wilcoxon test
**p value by log rank test for Serelaxin vs. Placebo; HR estimate by Cox model, HR<1.0 favors Serelaxin

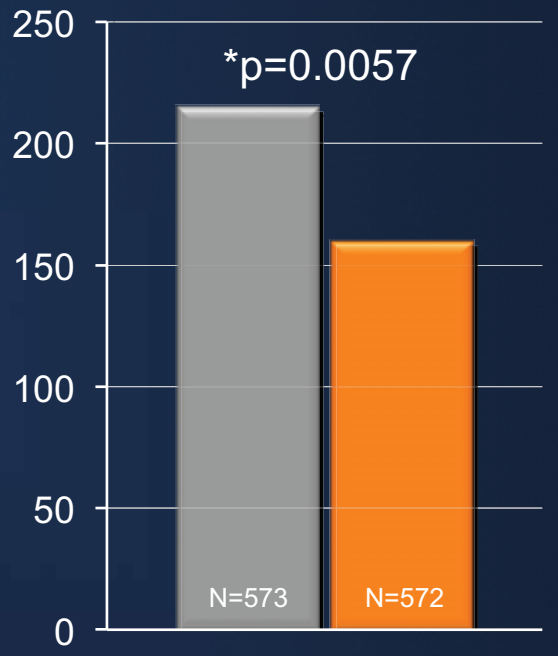
Intravenous Diuretic Use

Total daily dose IV diuretics (mg)

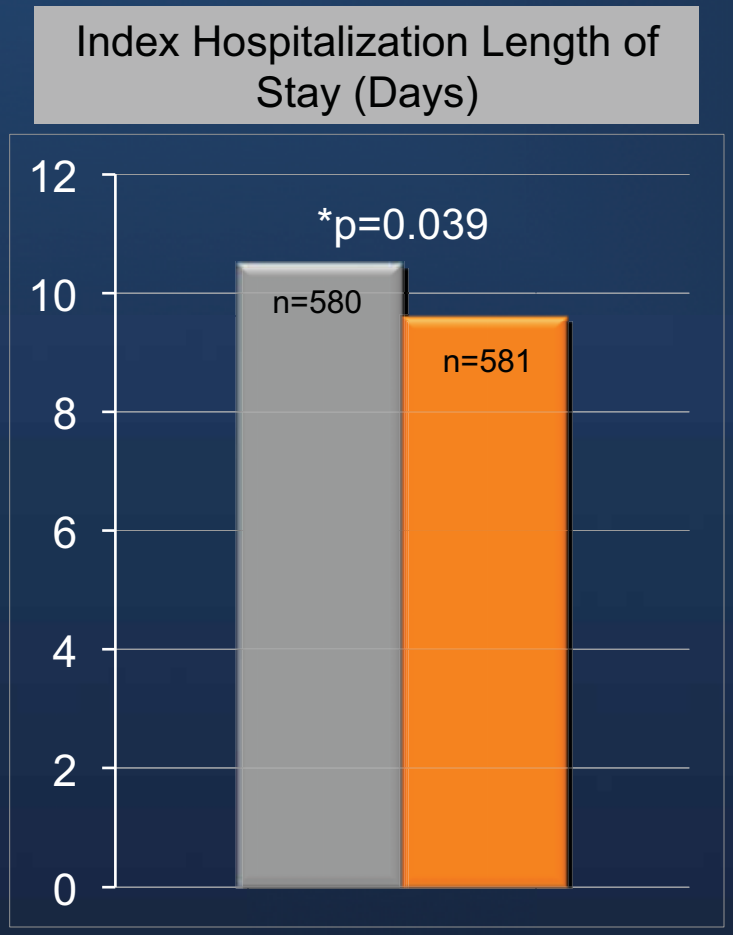


*p value by t test

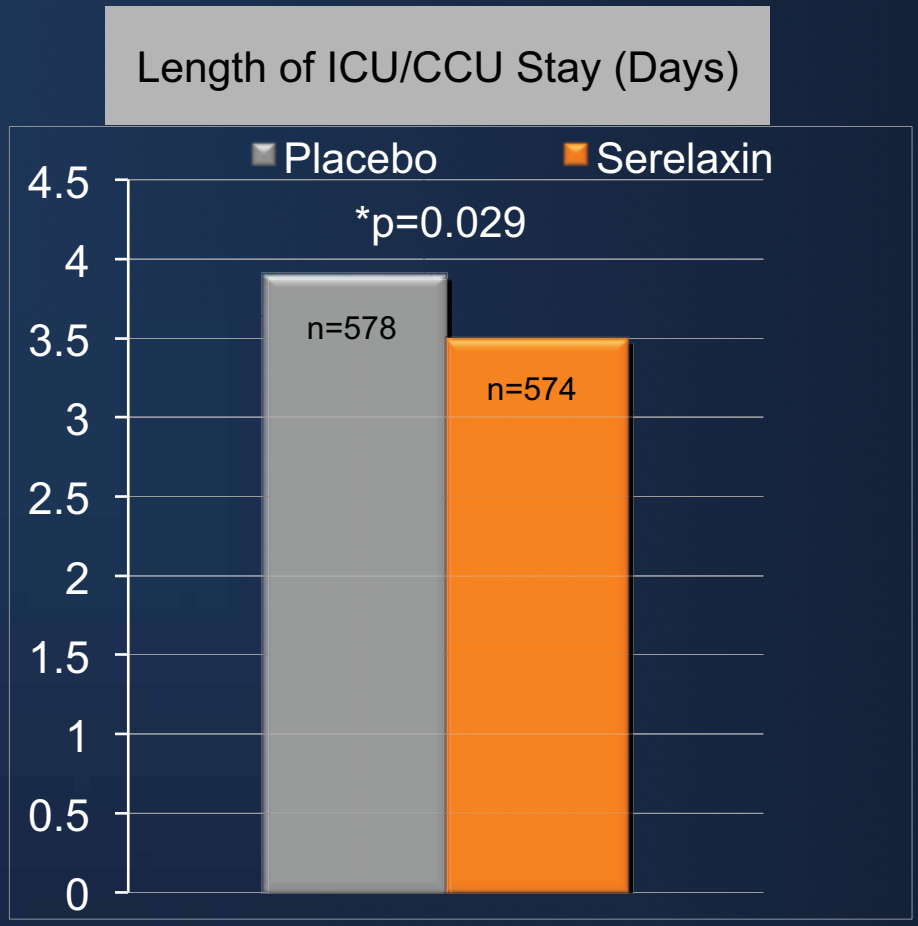
IV diuretics use (cumulative total dose from day 1-5 (mg))



Index Hospitalization LOS



Patients still in the hospital at Day 60 are censored at Day 60. Patients who died in-hospital are imputed as the maximum +1 day.



*p value by 2-sided Wilcoxon rank sum test

RELAX-AHF

Incidence of AEs/SAEs to Day 14

	Placebo (N=570) n (%)	Serelaxin (N=568) n (%)
Subjects with any AE	**320 (56.1)**	**305 (53.7)**
Subjects with any drug-related AE[1]	46 (8.1)	47 (8.3)
Subjects with AE leading to study drug d/c	22 (3.9)	26 (4.6)
Hypotension-related AE (through day 5)	25 (4.4)	28 (4.9)
Renal Impairment-related AE (through day 5)	49 (8.6)	26 (4.6)*
Subjects with any SAE	**78 (13.7)**	**86 (15.1)**
Subjects with any drug-related SAEs	2 (0.4)	3 (0.5)
Subjects with SAE leading to drug d/c	3 (0.5)	5 (0.9)
Serious AE with an outcome of death	15 (2.6)	10 (1.8)

The number of subjects with any AE includes all AEs and SAEs reported through Day 14.
Non-serious AEs were collected through Day 5, SAEs through Day 14

RELAX-AHF

Biomarkers

Criteria		Placebo	Serelaxin
NT-proBNP (≥30% decrease at Day 2)	Yes	315 (58.0%)	371 (69.0%)*
	No	228 (42.0%)	167 (31.0%)
Creatinine (≥0.3 mg/dl Increase at Day 2)	Yes	108 (19.8%)	59 (10.9%)**
	No	437 (81.2%)	482 (89.1%)
Troponin T (≥20% Increase at Day 2)	Yes	145 (27.2%)	86 (16.5%)**
	No	389 (72.8%)	436 (83.5%)
ALT (Change at Day 2)	mg/dL	-2.3	-6.4***

*p = 0.0002
**p < 0.0001
***p < 0.0010

Conclusions

In selected patients with AHF, early treatment with serelaxin for 48 h improved:

- Dyspnea relief: VAS AUC
- In-hospital signs and symptoms of AHF
- In-hospital end organ dysfunction/ damage
- In-hospital worsening of heart failure
- 180-day CV and all-cause mortality

…but had no effect on rehospitalizations.

Serelaxin use in AHF was safe with few hypotensive events and adverse events similar to placebo

Study Organization

- Co-PIs: M Metra (IT), JR Teerlink (US)
- Executive Committee: G Cotter (US), BA Davison (US), GM Felker (US), G Filipatos (GR), BH Greenberg (US), P Ponikowski (PL), TM Severin (CH), SL Teichman (US), E Unemori (USA), AA Voors (NL).
- Steering Committee: KF Adams (US), M Dorobantu (RO), L Grinfeld (AR), G Jondeau (FR), A Marmor (IL), J Masip (ES), PS Pang (US), K Werdan (DE).
- DSMB: BM Massie-Chair (US), M Böhm (DE), E Davis (US), G Francis (US), S Goldstein (US).
- Sponsor: Corthera, Inc. (a Novartis affiliate company)
- Coordinating Center: Momentum Research, Inc.

RELAX-AHF Investigators

- *Argentina (71 patients):* GM Ferrari; A Quiroga; A Fernandez; E Perna; MS Ramos; L Guzman; G Cursack; O Allall; MG Masuelli; C Rapallo.
- *France (21):* A Cohen-Solal; M Galinier; G Jondeau; R Isnard.
- *Germany (78):* H-G Olbrich; V Mitrovic; K Werdan; S Felix; T Heitzer; G Cieslinski; K Stangl.
- *Hungary (151):* J Tomcsányi; D Apró; K Tóth; A Vértes; G Lupkovics; Z László; A Cziraki.
- *Israel (210):* A Marmor; S Goland; A Katz; R Zimlichman; D Aronson; A Butnaru; M Omary; XA Piltz; D Zahger.
- *Italy (77):* M Metra; A Mortara; M Balbi; F Cosmi; S DiSomma; MC Brunazzi.
- *Netherlands (10):* AA Voors; PEF Bendermacher; G-J Milhous; PL van Haelst; P Dunselman.
- *Poland (258):* P Ponikowski; P Jankowski; A Wysokinski; M Dluzniewski; J Stepinska; W Tracz; M Krzeminska-Pakula; J Grzybowski; K Loboz-Grudzien.
- *Romania (153):* D-D Ionescu; CS Stamate; M Dorobantu; C Pop; A Matei; T Nanea; M Radoi; A Salajan.
- *Spain (18):* J Masip; D Pascual; MG Bueno; R Muñoz.
- *United States of America (114):* S Meymandi; P Levy; PS Pang; C Clark; G Fermann; KF Adams, Jr.; B Bozkurt; J Fulmer; D Mancini; T Vittorio; R Zolty; BH Greenberg; E Chung; V Florea; J Heilman III; A Storrow; MR Costanzo; G Lamas; M Greenspan; M Klapholz; J Martinez-Arraras; WF Peacock; N Saleh; R Small; JR Teerlink; D Wencker.


RELAX-AHF