A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study to Assess the Tolerability and Pharmacodynamic Effects of CRD-740, a PDE9 Inhibitor, in Participants with Chronic Heart Failure

The CARDINAL-HF Trial

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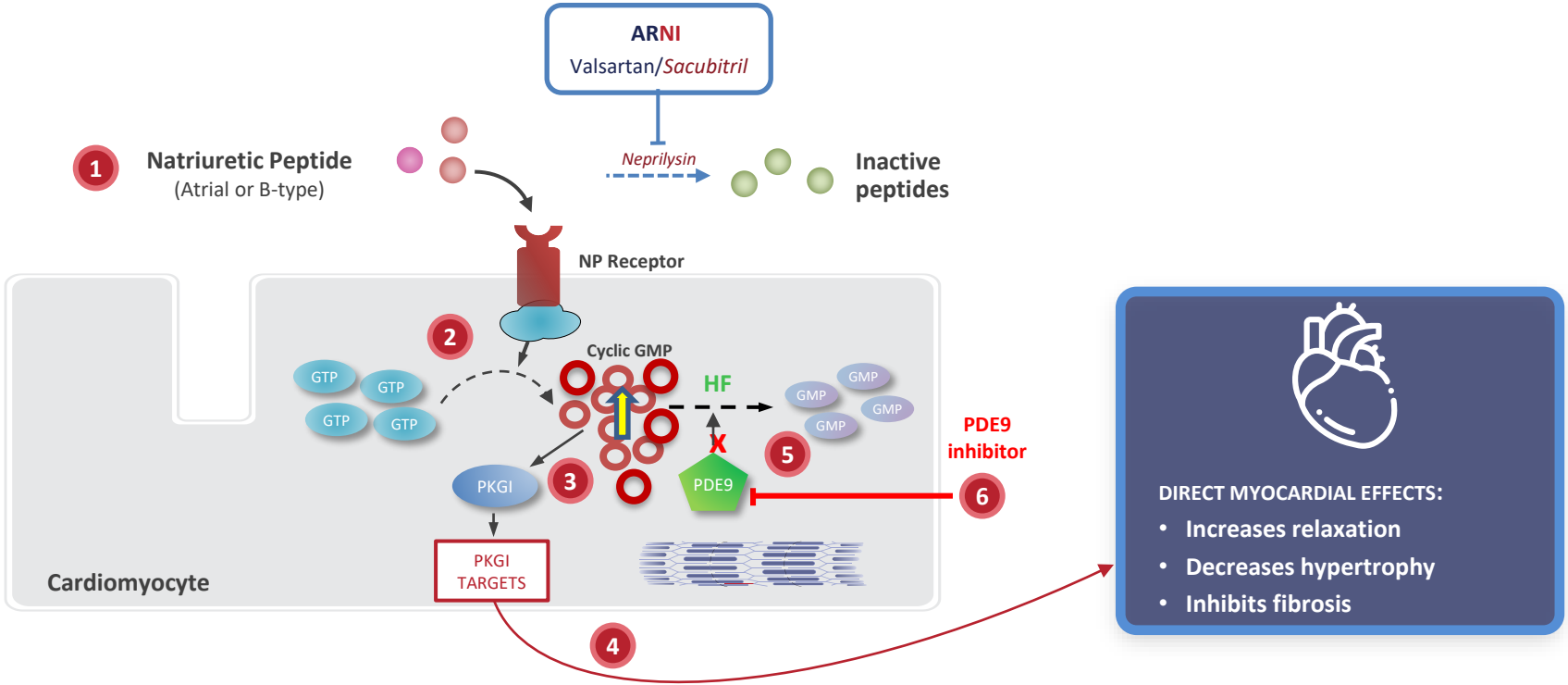
Disclosures

- Trial sponsored by Cardurion Pharmaceuticals, Inc.
- All investigators and/or institutions received support from Cardurion for trial activities.
- JU, SS and JM receive support as members of the Cardurion clinical advisory board.
- HS is an employee and stockholder in Cardurion

Natriuretic Peptide Signaling Enhances Cardiac Function
PDE9 Selectively Inhibits this Pathway



ARNI= angiotensin II receptor antagonist/neprilysin inhibitor, NP= natriuretic peptide, GMP= guanosine monophosphate, GTP= guanosine triphosphate, PKG= protein kinase G, PDE9= phosphodiesterase 9

CRD-740: Small Molecule PDE9 Inhibitor

- Potent and specific inhibitor of PDE9
- Previously studied in healthy volunteers and trials of Alzheimer's disease and sickle cell disease, more than 250 humans exposed
- No adverse drug reactions noted to date
- High bioavailability with low plasma protein binding
- 25mg BID dose yields plasma concentrations 135-fold above the PDE9 IC_{50} at C_{max} and 19-fold above the PDE9 IC_{50} at C_{trough}

Trial Objectives

- **Primary Objectives:**
  - **To assess the safety and tolerability of CRD-740 in pts with HFrEF**
  - **To assess the effect of CRD-740 compared to placebo on plasma cGMP at Week 4**

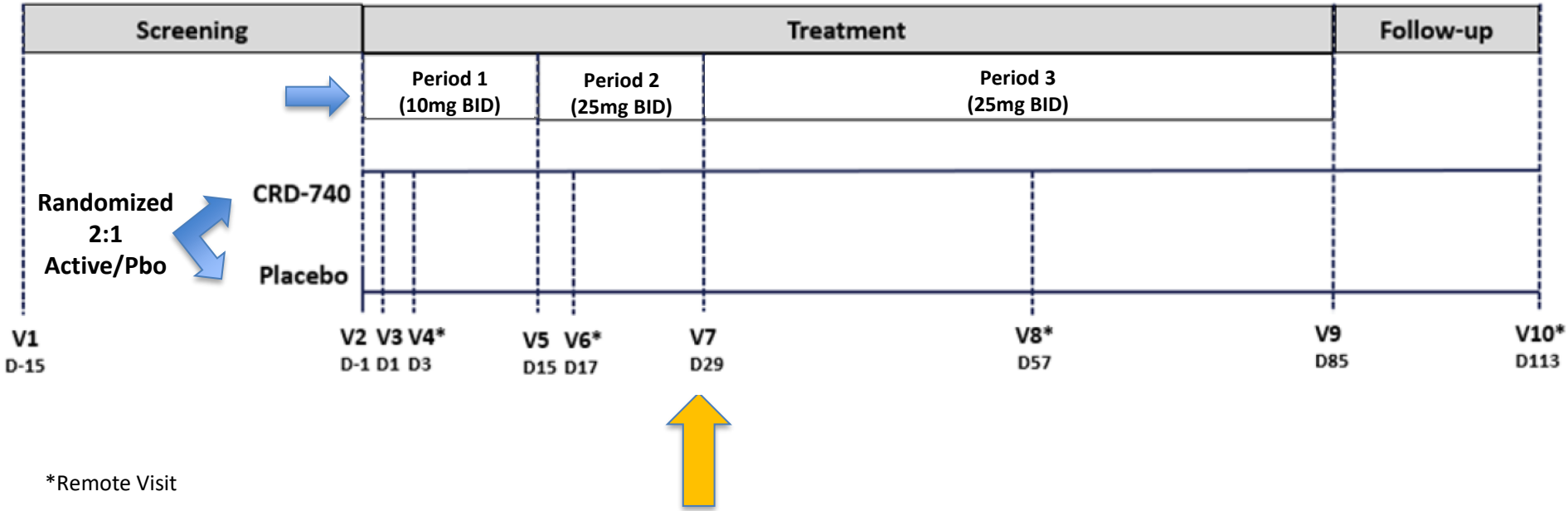
- **Secondary Objective:**
  - **To assess the pharmacokinetics of CRD-740 in pts with HFrEF**

- **Exploratory Objectives- compare the effects of CRD-740 vs. placebo on:**
  - **urinary cGMP at Week 4**
  - **KCCQ-23 scores at Week 12**
  - **the proportion of pts with ≥5-point improvement in the KCCQ-23-CS at Week 12**
  - **NT-proBNP at each CRD-740 dose and time-point**

Key Inclusion & Exclusion Criteria

- **Key Inclusion Criteria:**
  - **Adult subjects ≥18 yrs of age**
  - **Evidence of clinical HF syndrome, NYHA Class II – III**
  - **LVEF ≤40% by echo at screening**
  - **NT-proBNP level ≥600 pg/ml at screening (≥1000 pg/mL with AFIB/Flutter)**
  - **Stable doses of GDMT for a minimum of 4 weeks prior to screening**
- **Key Exclusion Criteria:**
  - **Recent HF exacerbation defined by hospitalization or requirement for IV diuretics within 60 days of screening**
  - **Chronic treatment with PDE5 inhibitors**
  - **Estimated GFR <30 mL/min/1.73m^2**

Trial Design Schematic



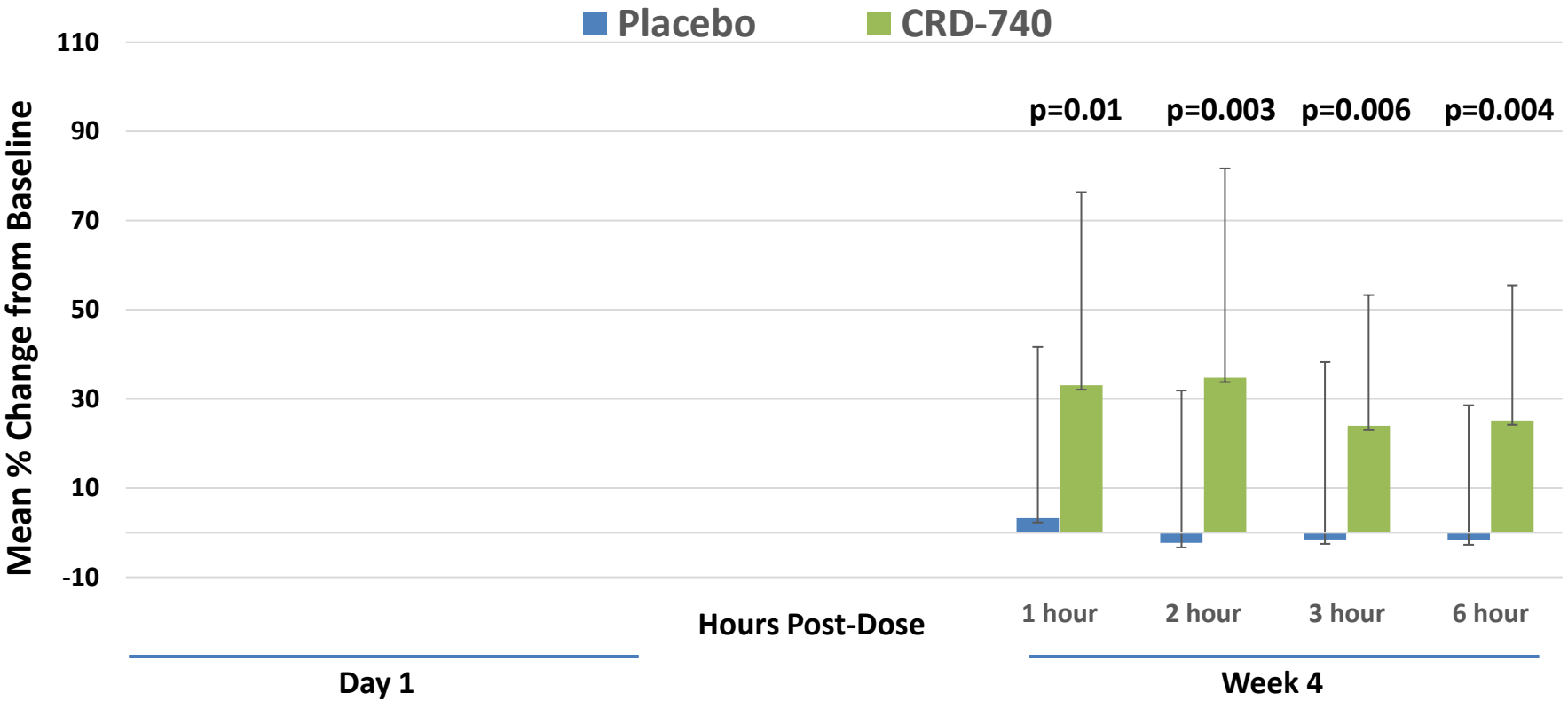
*Remote Visit

Primary Endpoint

Demographics and Baseline Characteristics (ITT Population)

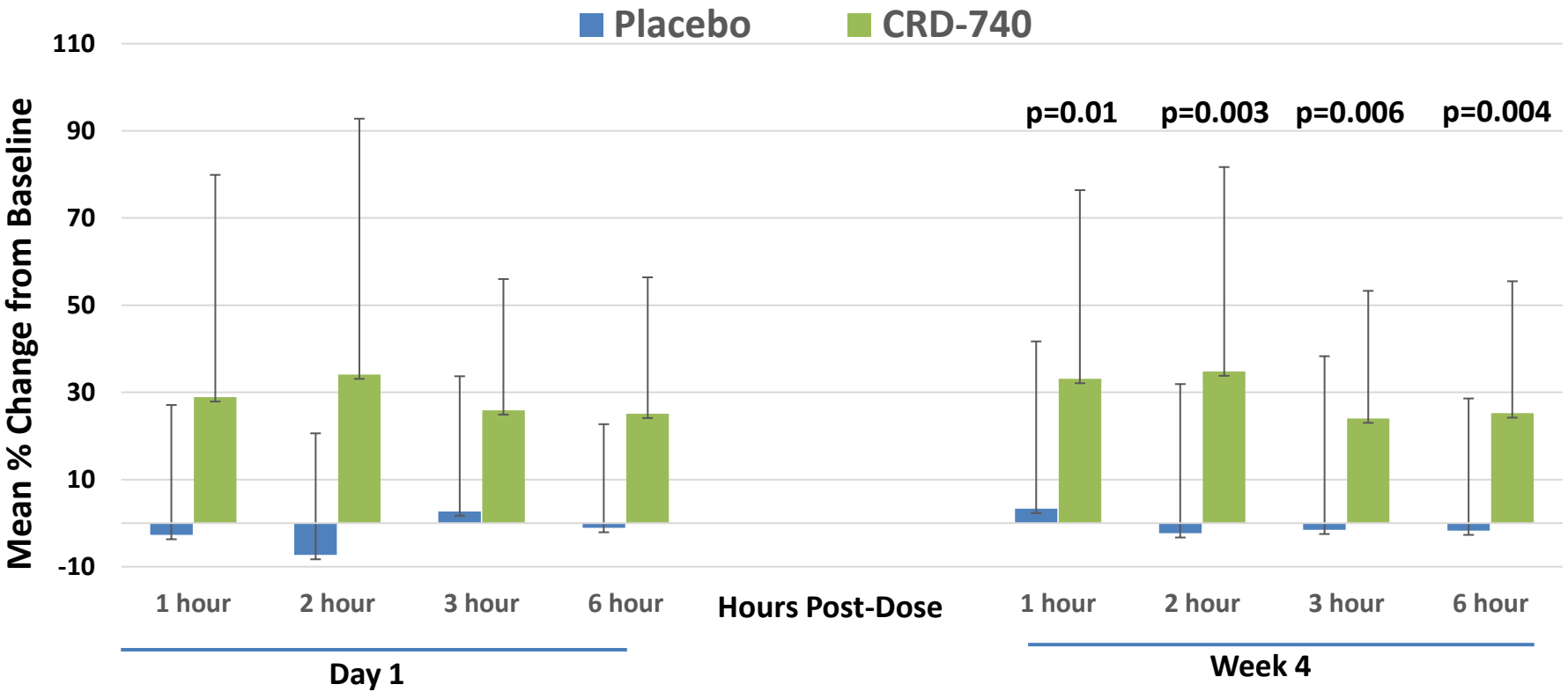
	CRD-740 (n=40)	Placebo (n=20)
Age, mean (SD)	**68.4 (12.7)**	**65.6 (13.2)**
Race, n (%)		
White	**29 (73%)**	**15 (75%)**
Black or African American	**9 (23%)**	**4 (20%)**
Asian	**2 (5%)**	**1 (5%)**
Sex, n (%)		
Male	**35 (88)**	**16 (80)**
Female	**5 (13)**	**4 (20)**
BMI (kg/m^2), mean (SD)	**31.4 (11.5)**	**28.4 (6.0)**
Sacubitril/Valsartan, n (%)	**29 (73%)**	**15 (75%)**
SGLT2 Inhibitor, n (%)	**22 (55%)**	**6 (30%)**
LVEF at Screening, mean (SD)	**29% (7.2)**	**27% (6.2)**

Time-matched Change From Baseline in Plasma cGMP (mITT)



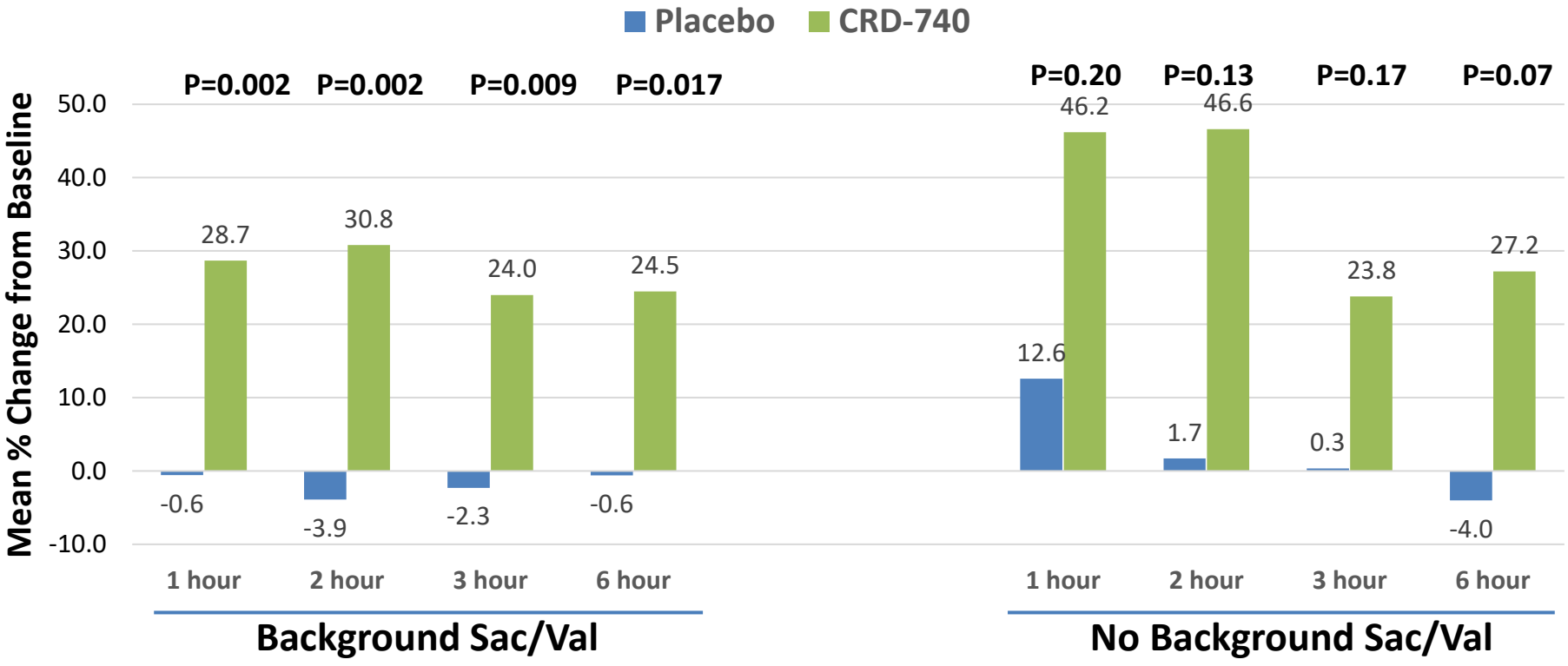
cGMP change calculated as AUC for the 0-6 hr timepoints was also significantly greater in CRD-740 vs pbo (p=0.007 at week 4)

Time-matched Change From Baseline in Plasma cGMP (mITT)



Time-matched % Change from Baseline in Plasma cGMP at Week 4 (mITT)

Background Sacubitril/Valsartan vs No Background Sacubitril/Valsartan



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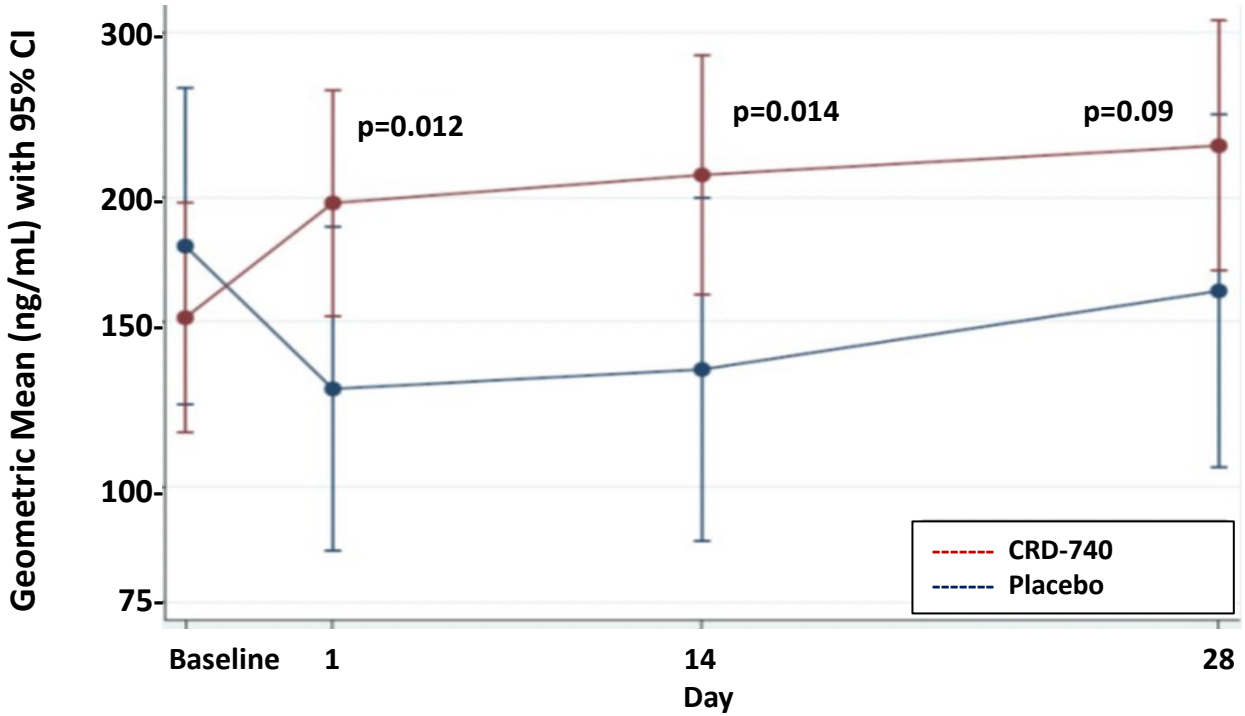
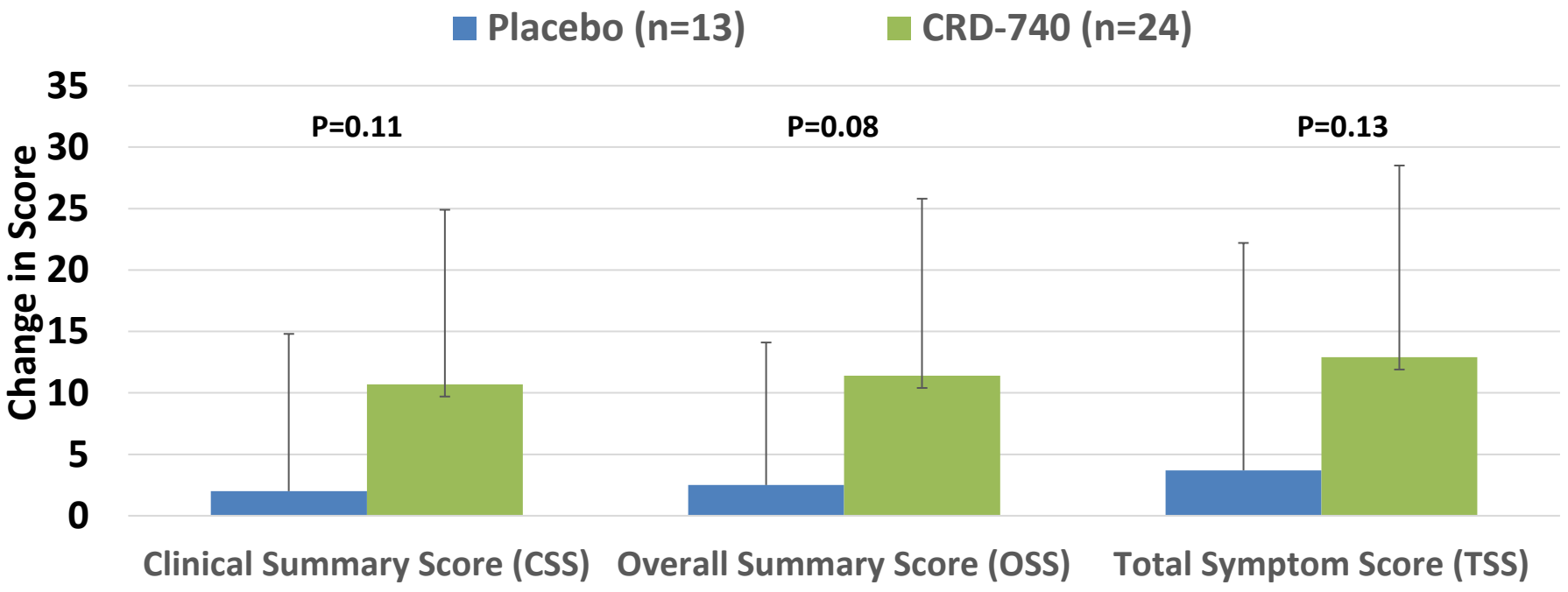
*Post-hoc analysis

Urinary cGMP Over Time in CARDINAL-HF (mITT) (6-hour Urine Collection)

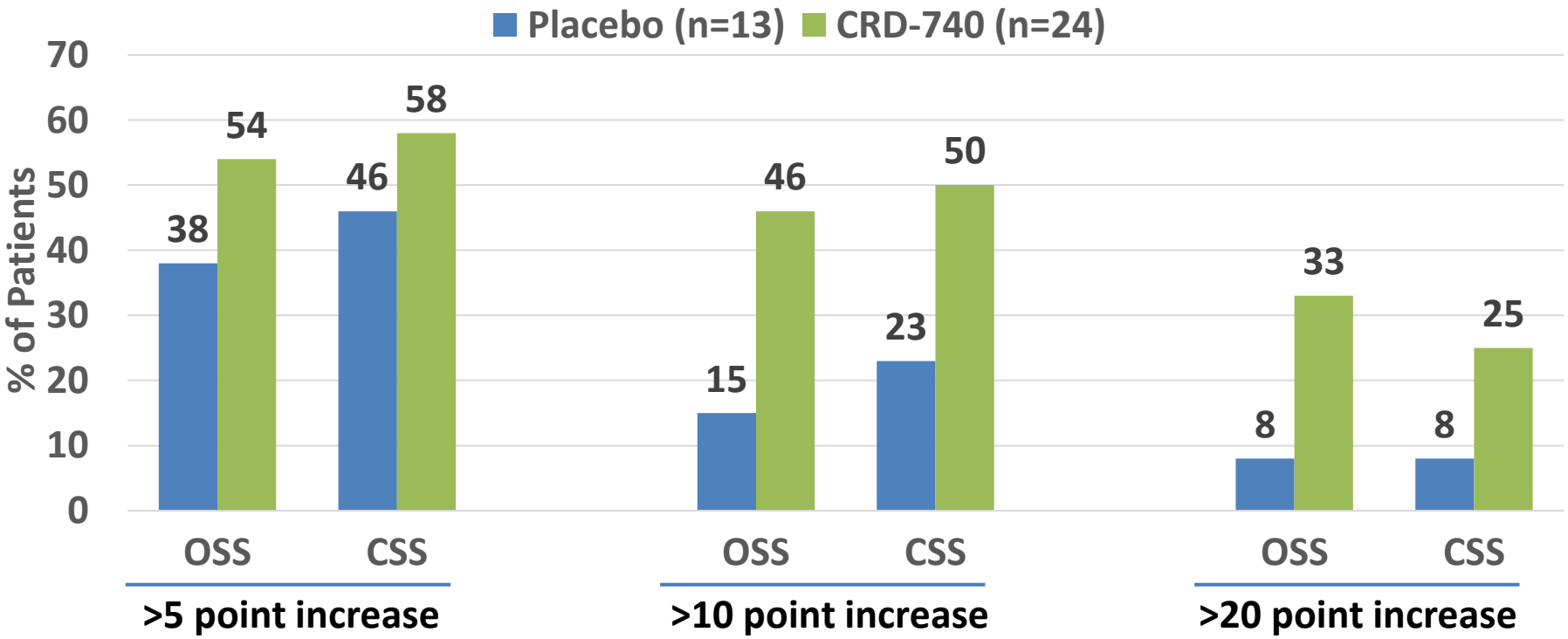


p-value represents comparison between CRD-740 and placebo

Mean Change in KCCQ from Baseline at Week 12 (mITT)



KCCQ Summary Scores: Categorical Changes at Week 12 (mITT)



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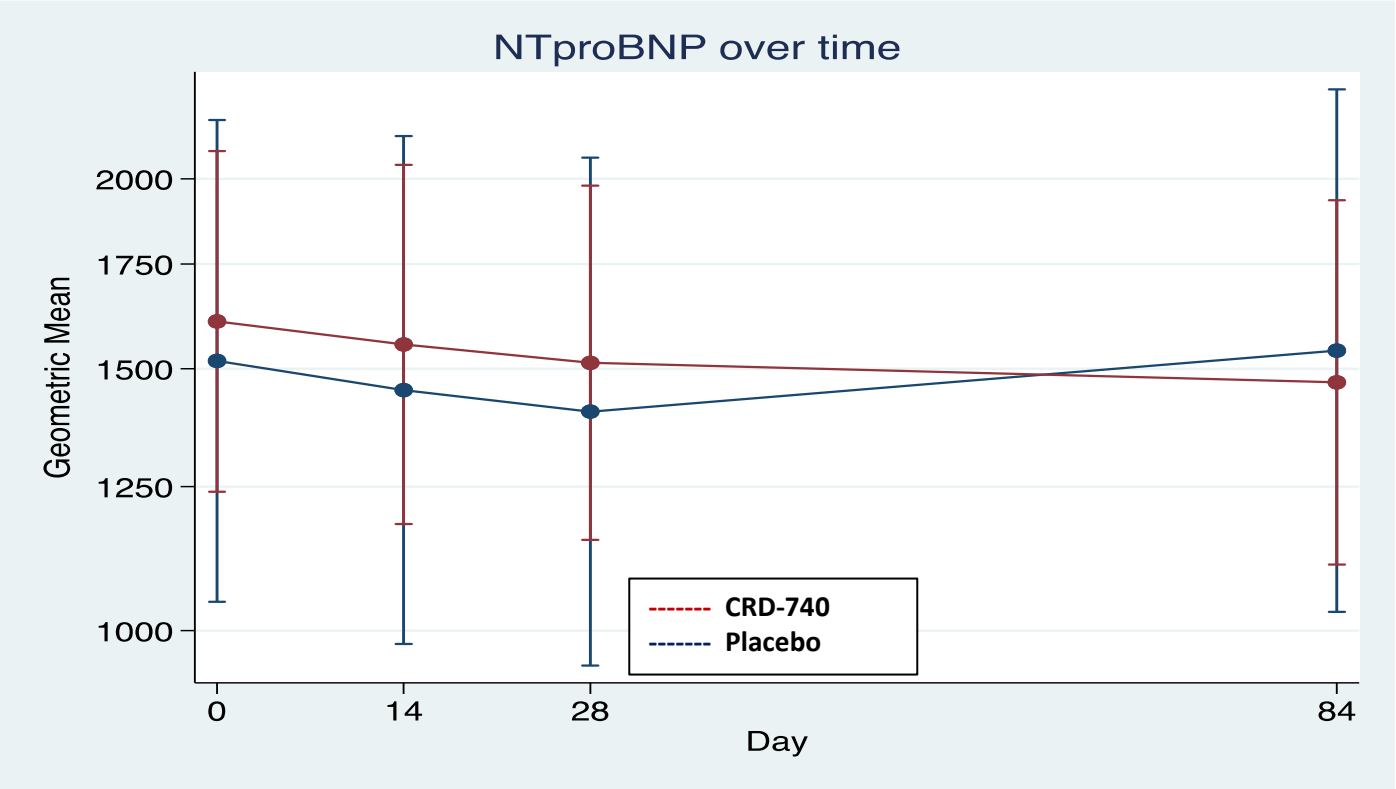
*Post-hoc analysis; > 10 point and > 20 point increase

Change in NT-proBNP Over the Course of the Trial, mITT (pg/mL)



*Geometric Mean with 95% CI

Summary of TEAEs, Vital Signs and Lab Changes (safety population)

Adverse Events	CRD-740 (n=40) n (%)	Placebo (n=20) n (%)
Any Study Treatment Related TEAE	**5 (12.5%)**	**3 (15%)**
Leading to discontinuation of study treatment	**1 (2.5%)**	**0**
Leading to death	**0**	**0**
Any Serious TEAE	**3 (7.5%)**	**3 (15%)**
Leading to discontinuation of study treatment	**1 (2.5%)**	**2 (10%)**
Labs and Vital Signs	**CRD-740 (n=40)**	**Placebo (n=20)**
Serum Cr (µmol/L) Baseline, Mean (SD)	**114 (30)**	**111 (23)**
Change at week 12	**7 (16)**	**6 (16)**
Systolic BP (mmHg) Baseline, Mean (SD)	**120 (14)**	**116 (17)**
Change at week 12	**4 (23)**	**0 (15)**

Limitations

- **Pilot trial with modest number of patients**
- **Safety/tolerability signals are early, require larger sample sizes**
- **Larger trial and increased power will be necessary to adequately explore clinical and biomarker endpoints.**

Conclusions

In this cohort with HFrEF:

- **PDE9 inhibition with CRD-740 was well tolerated over 12 weeks**
- **Elevations in plasma and urine cGMP demonstrate target engagement**
- **Similar cGMP elevations seen in those on vs. not on sacubitril/valsartan suggesting potential additivity**
- **Directionally favorable signals seen in KCCQ scales**
- **The data support that PDE9 inhibition may enhance the favorable effects of the NP signaling system on cardiac function in HF**

- **This study sets the stage for larger global PDE9 inhibitor phase 2 trials across the LVEF spectrum, which are now underway***

*NCT06215911, NCT06215586