Preliminary

# EMBRACE STEMI


**A phase 2a, randomized, double-blind, placebo-controlled trial to evaluate the safety, tolerability, and efficacy of intravenous Bendavia on reperfusion injury in patients treated with standard therapy including primary percutaneous coronary intervention and stenting for ST-segment elevation myocardial infarction**

**C. Michael Gibson, M.S., M.D. on behalf of the EMBRACE STEMI Investigators**

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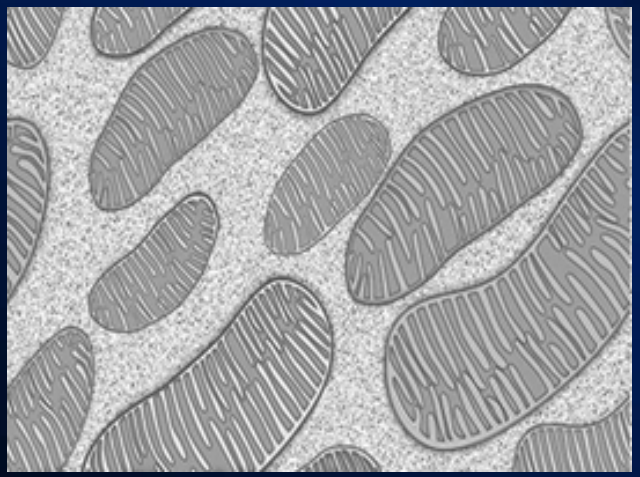
# Disclosure

Dr. Gibson and the PERFUSE study group received research grant support for the EMBRACE trial from the sponsor Stealth Pharmaceuticals which was paid to the Beth Israel Deaconess Medical Center

# Bendavia Reduces ROS Generation, Protects Cardiolipin, and Preserves Mitochondrial Integrity and Function in Animal Models



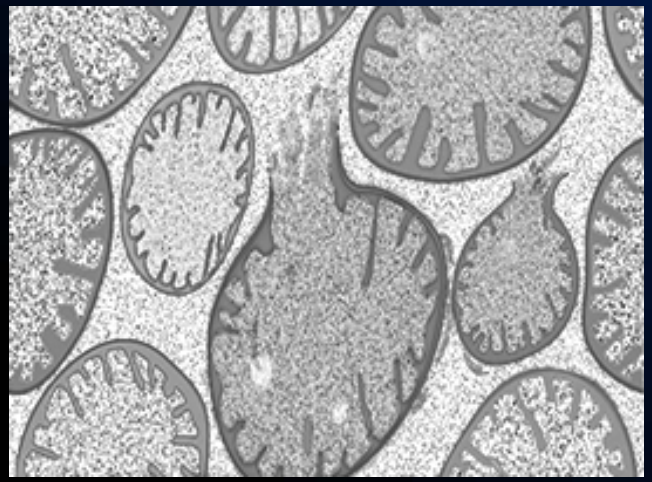
Reperfusion

↓ **Bendavia**

Reduces Reactive Oxygen Species (ROS)

↓ **Bendavia**

Preserves mitochondrial lipids & cardiolipin



Positively impacts integrity, electron transport, & bioenergetics of mitochondria

↓

Reduces infarct size 10%-40%

Brown *et al*. *Pharmacol Ther.* 2013;140(3):258-66

# Bendavia in Heart Failure

## Canine Heart Failure Model

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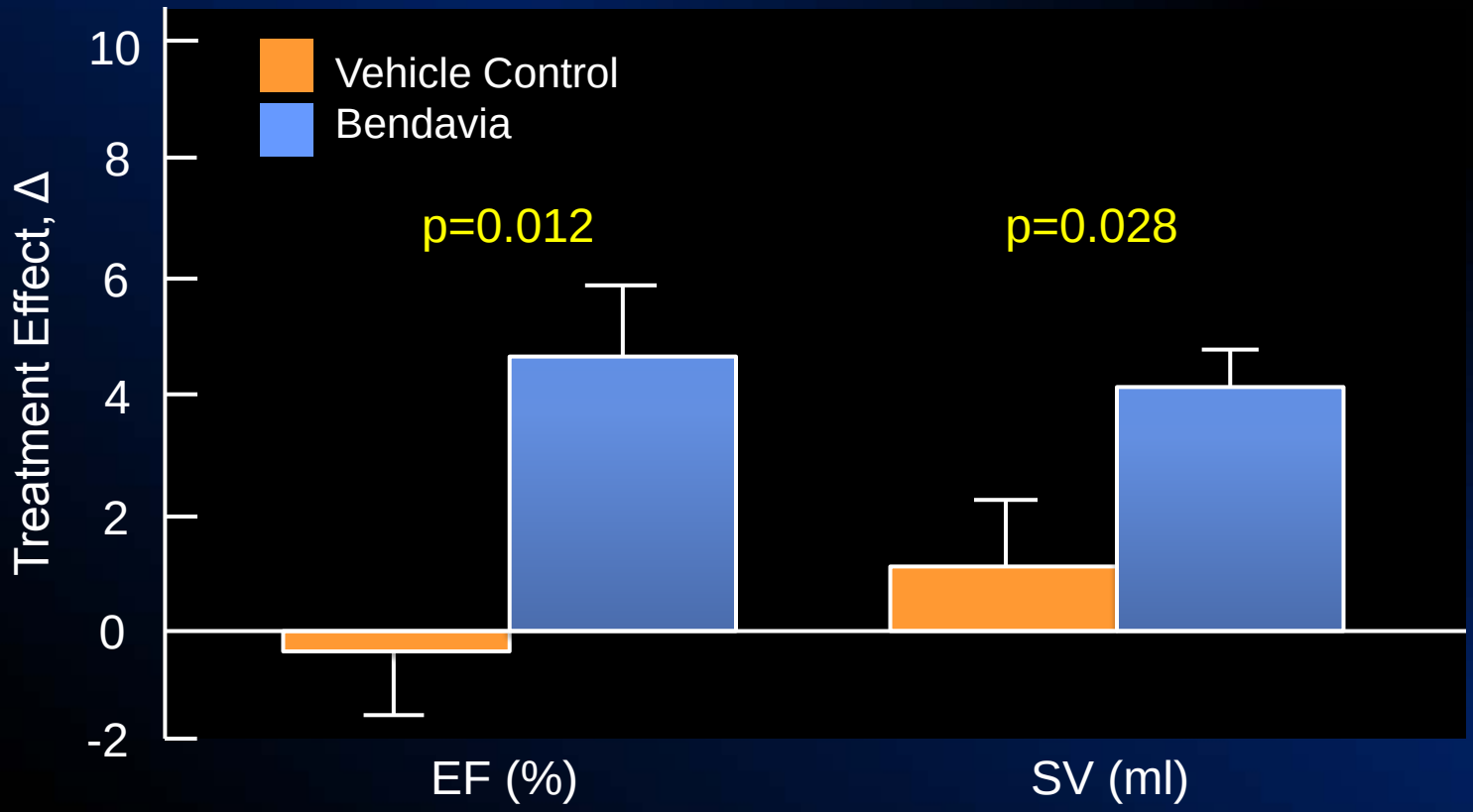
Dose similar to EMBRACE STEMI (0.05 mg/kg/h) for 2 hours




**No Change in HR**
**No Change in BP**

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Sabbah *et al.* *Eur Heart J.* 2013 Suppl I;34:610

# EMBRACE STEMI Trial Design

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## Patients with First Anterior STEMI

TIMI 0/1 flow in prox or mid LAD, anticipated Sx to PCI <4 hrs, shock

R 1:1 Blinded

| **Volume-matched IV Placebo** (N=147) | **Bendavia IV at 0.05 mg/kg/hr** (N=150) |
|---|---|

Administered > 15 min pre PCI & 60 min post

**Primary Endpoint:** AUC for CK-MB over initial 72h post PCI

**Clinical Endpoint:** Composite of all cause death, new onset CHF >24h post-PCI within index hospitalization, and CHF rehospitalization

# EMBRACE STEMI: Secondary Endpoints

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- Infarct size by AUC for troponin I
- MRI infarct volume, LV mass, function and volume
- TIMI perfusion grade (TMPG) and corrected TIMI frame count (TFC) post-PCI
- ST-elevation resolution immediately post-PCI and 24-hour post

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# Trial Organization

**Trial Leadership: PERFUSE Study Group**

**Study Chairman: C. Michael Gibson**

**Co-Investigator: Douglas Weaver, Anjan Chakrabarti, Yazan Daaboul, Rim Halaby, Serge Korjian**

**PERFUSE Project Managers: Madeleine Cochet, Maria Stepanchak**

**PERFUSE Data Coordinating Ctr: Kathryn Spielman, Ana Florea, Brandon Neal**

**Executive Committee (EC):**

**Robert Kloner, Robert Giugliano, Christoph Bode, Michal Tendera, Andras Janosi**

**Data Safety Monitoring Board (DSMB):**

**Jeffrey Anderson, Carol Francisco, Samir Parikh, Stephen Textor**

**ECG and Angiography Core Labs: PERFUSE Study Group**

**Sponsor: Stealth BioTherapeutics**

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# Enrollment

| Poland (143) | Hungary (115) | Germany (38) | United States (4) |
|---|---|---|---|
| J Godlewski | B. Merkely | I. Ahrens | M. Del Core |
| S. Dobzycki | R. Kiss | C. Stellbrink | A. Khandelwal |
| J. Kochman | G. Lupkovics | R. Zotz | |
| K. Loboz-Grudzien | L. Toth | T. Schaeufele | |
| A. Ochala | Z. Piroth | K. Tiroch | |
| J. Peruga | | C. Skurk | |
| W. Pluta | | | |
| A. Kleinrok | | | |
| M. Dabrowski | | | |
| Z. Chmielak | | | |
| S. Bartus | | | |

**4 Countries** **24 Sites**

# Primary Analysis Population

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| | | Placebo | Bendavia |
|---|---|---|---|
| **N = 297** Randomized & Treated | | | |
| N = 288 | **N = 9** Failed Eligibility Criteria | 7 | 2 |
| N = 271 | **N = 17** Did Not Have Proximal or Mid LAD | 5 | 12 |
| N = 246 | **N = 25** Other Anatomical Exclusions | 12 | 13 |
| N = 129 | **N = 117** Pre-PCI TIMI Flow Grade > 1 | 58 | 59 |
| N = 122 | **N = 7** Insufficient Treatment Duration | 3 | 4 |
| N = 120 | **N = 2** Unsuccessful PCI, Post PCI TIMI < 2 | 1 | 1 |
| **N = 118** Primary Analysis Population | **N = 2** 2nd MI Within 72 Hours | 1 | 1 |

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# Baseline Characteristics

Preliminary

| | Placebo (N=60) | Bendavia (N=58) | p-value |
|---|---|---|---|
| **Clinical Characteristics** | | | |
| Age, mean ± SD | 61.3 ± 10.7 | 58.9 ± 10.8 | NS |
| Male, % (n) | 78.3% (47) | 65.5% (38) | 0.12 |
| Diabetes mellitus, % (n) | 13.3% (8) | 5.2% (3) | 0.13 |
| Hypertension, % (n) | 60% (36) | 37.9% (22) | 0.02 |
| Dyslipidemia, % (n) | 20% (12) | 8.6 (5) | 0.08 |
| Statin use prior to infarct, % (n) | 10% (6) | 5.2% (3) | NS |
| Active smoking, % (n) | 46.7% (28) | 36.2% (21) | NS |
| **Angiographic Characteristics** | | | |
| Ischemia time (min), median (IQR) | 151.5 (124.5, 203.5) | 151 (120, 210) | NS |
| LAD area at risk (%) , median (IQR) | 86% (79, 90) | 83% (78, 89) | NS |
| Arterial diameter (mm), median (IQR) | 2.86 (2.57, 3.19) | 2.97 (2.60, 3.35) | NS |
| Pre-PCI aspiration | 71.7% (43) | 65.5% (38) | NS |

Values provided for the primary analysis population

# Results: Primary Endpoint AUC CK-MB$_{(0\text{-}72h)}$

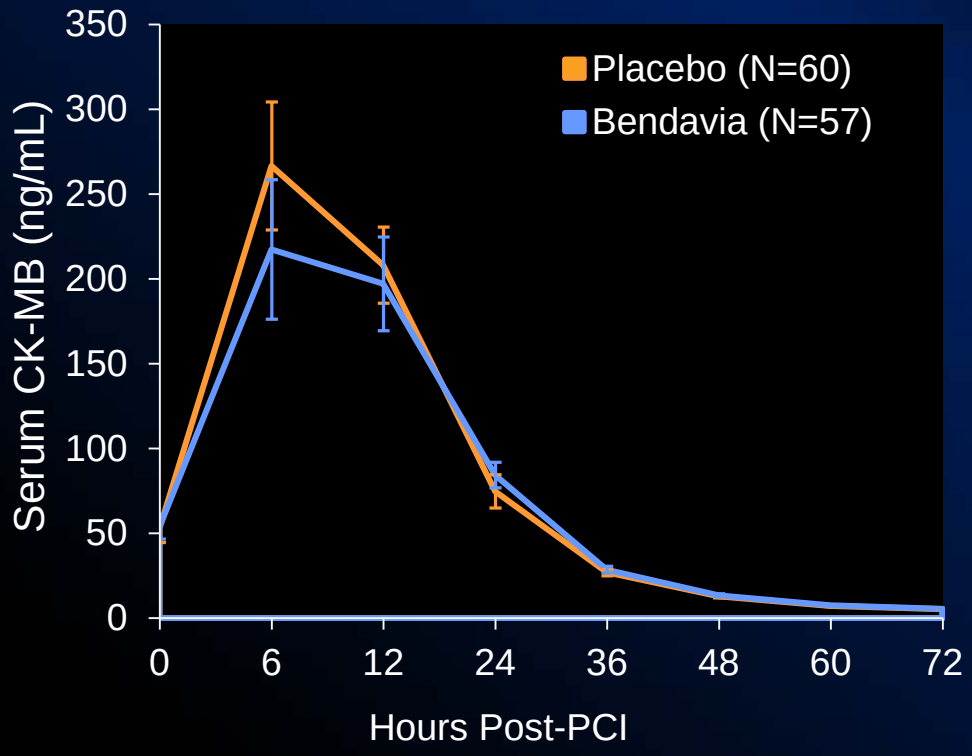
Preliminary

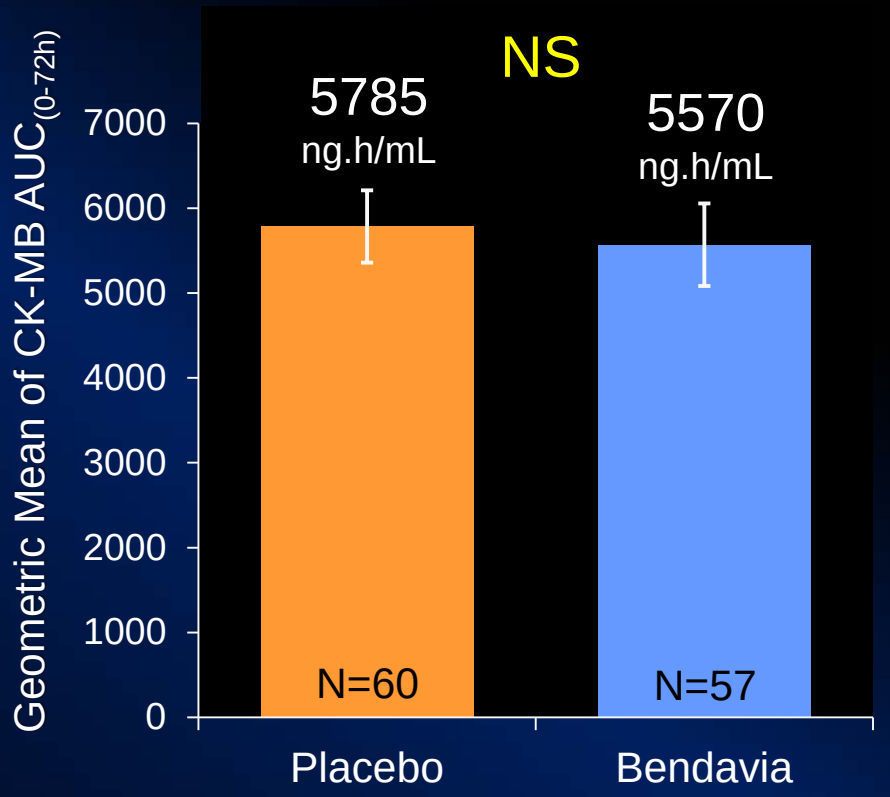
**CK-MB at 6 hours**

Placebo: 266.6 ± 37.7 ng/mL

Bendavia: 217.4 ± 41.1 ng/mL

NS




AUC CK-MB provided for the primary analysis population excluding subjects with insufficient CK-MB results. AUC CK-MB is log-transformed prior to analysis. Covariates include symptom-onset to PCI and lesion location relative to the length of the culprit artery.

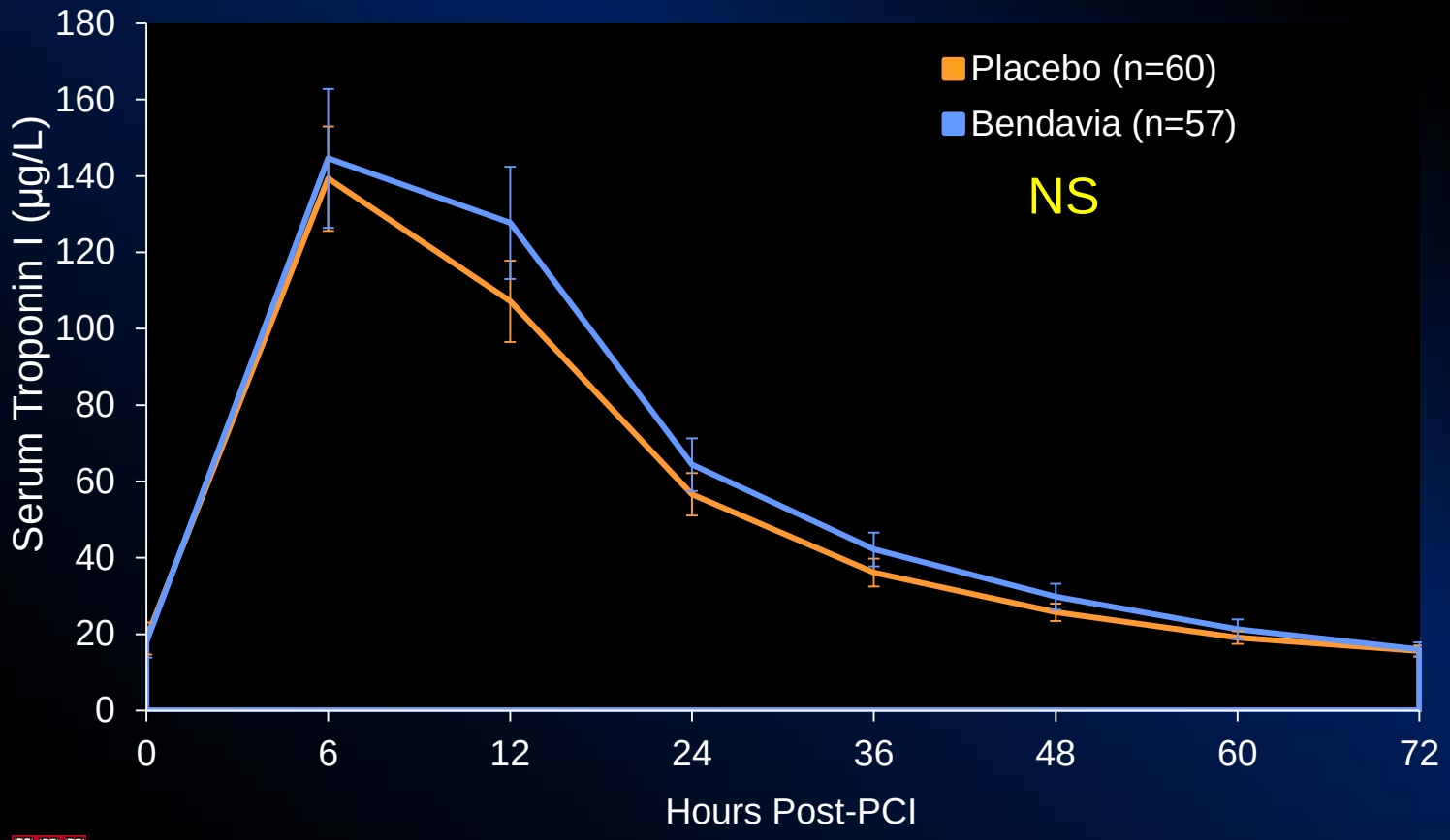
# Results: AUC TnI$_{(0\text{-}72h)}$

Preliminary

**TnI at 6 hours**

Placebo: 139.3 ± 13.7 µg/L NS

Bendavia: 144.6 ± 18.2 µg/L




AUC TnI provided for the primary analysis population excluding subjects with insufficient TnI results. AUC TnI is log-transformed prior to analysis. Covariates include symptom-onset to PCI and lesion location relative to the length of the culprit artery

# Results: Cardiac MRI at 4 ± 1 Days Post-PCI

Preliminary

| | Placebo | Bendavia | p-value |
|---|---|---|---|
| Infarct Volume (ml) | 48.4 ± 28.0 (N=54) | 43.1 ± 23.4 (N=51) | NS |
| Total LV Mass (g) | 162.2 ± 52.4 (N=48) | 141.5 ± 53.2 (N=45) | 0.08 |
| Infarct Vol / Total LV Mass (%) | 28.7 ± 11.1 (N=48) | 30.9 ± 12.0 (N=45) | NS |
| Edema Volume (ml) | 58.0 ± 23.0 (N=55) | 55.0 ± 26.0 (N=53) | NS |
| LV End-Diastolic Volume (ml) | 90.0 ± 19.2 (N=54) | 92.5 ± 19.8 (N=50) | NS |
| LV End-Systolic Volume (ml) | 53.4 ± 16.9 (N=54) | 53.1 ± 19.7 (N=50) | NS |
| LV Ejection Fraction (%) | 41.9 ± 10.4 (N=55) | 44.0 ± 11.0 (N=52) | NS |

Values provided for the primary analysis population.
P-values are reported for model adjusted for symptom onset to PCI and location of lesion relative to the length of the culprit artery.

# Results: Cardiac MRI at 30 ± 7 Days Post-PCI

Preliminary

| | Placebo | Bendavia | p-value |
|---|---|---|---|
| Infarct Volume (ml) | 31.5 ± 18.2 (N=53) | 30.1 ± 14.9 (N=48) | NS |
| Total LV Mass (g) | 141.9 ± 45.1 (N=47) | 125.1± 46.6 (N=47) | 0.17 |
| Infarct Vol / Total LV Mass (%) | 22.5 ± 9.1 (N=47) | 24.2 ± 8.7 (N=46) | NS |
| Edema Volume (ml) | 40.0 ± 25.0 (N=52) | 36.0 ± 21.0 (N=45) | NS |
| LV End-Diastolic Volume (ml) | 95.6 ± 23.1 (N=52) | 99.3 ± 22.0 (N=46) | NS |
| LV End-Systolic Volume (ml) | 54.1 ± 19.8 (N=52) | 54.4 ± 18.4 (N=46) | NS |
| LV Ejection Fraction (%) | 44.8 ± 10.9 (N=53) | 46.1 ± 9.1 (N=48) | NS |

Values provided for the primary analysis population.
P-values are reported for model adjusted for symptom onset to PCI and location of lesion relative to the length of the culprit artery.

# Results: ST-Segment Resolution

Preliminary

| | Placebo | Bendavia | p-value |
|---|---|---|---|
| **ST Resolution Immediately Post-PCI** | | | |
| Absent (<30%) | 39% (23/59) | 40% (22/55) | NS |
| Partial (30-70%) | 39% (23/59) | 45.4% (25/55) | |
| Complete (≥70%) | 22% (13/59) | 14.6% (8/55) | |
| **ST Resolution 24 Hours Post-PCI** | | | |
| Absent (<30%) | 12.3% (7/57) | 7.1% (4/56) | NS |
| Partial (30-70%) | 36.8% (21/57) | 39.3% (22/56) | |
| Complete (≥70%) | 50.9% (29/57) | 53.6% (30/56) | |

Values provided for the primary analysis population plus either all subjects with a second MI within 72 hours (for the analysis of the immediate ST-segment resolution) or subjects with a second MI after 24 hours (for the analysis of the 24-hours ST-segment resolution).
ST-segment resolution was analyzed with embolus aspiration, time from symptoms onset to PCI, and location of lesion as stratification variables.

# Results: Post PCI Angiographic Findings

Preliminary

| | Placebo | Bendavia | p-value |
|---|---|---|---|
| **TIMI Flow Grade** | | | |
| TFG ≤ 2 | 12.9% (8/62) | 11.7% (7/60) | NS |
| TFG 3 | 87.1% (54/62) | 88.3% (53/60) | |
| **TIMI Frame Count** | | | |
| Corrected TFC, median (IQR) | 51 (41, 78) (N=53) | 51 (39, 82) (N=58) | NS |
| **TIMI Myocardial Perfusion Grade** | | | |
| TMPG 0-1 | 53.3% (32/60) | 59.3% (35/59) | NS |
| TMPG 2-3 | 46.7% (28/60) | 40.7% (24/59) | |

Values provided for the primary analysis population plus subjects with post-PCI TIMI Flow Grade < 2 and subjects with second MI within 72 hours

# Results: Clinical Composite Endpoint

Preliminary

| | Placebo (N=60) | Bendavia (N=58) | p-value |
|---|---|---|---|
| **30 ± 7 days** | | | |
| Death, new-onset CHF >24h post PCI, CHF rehospitalization, % (n) | 5.0% (3) | 8.6% (5) | NS |
| Death, new-onset CHF, CHF rehospitalization, % (n) | 28.3% (17) | 22.4% (13) | NS |
| **6 ± 1.5 months** | | | |
| Death, new-onset CHF >24h post PCI, CHF rehospitalization, % (n) | 8.3% (5) | 12.1% (7) | NS |
| Death, new-onset CHF, CHF rehospitalization, % (n) | 28.3% (17) | 25.9% (15) | NS |

Values provided for primary analysis population

# Clinical Events: Congestive Heart Failure Within 24 Hours Post PCI

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**75% (23/31) of new-onset CHF events occurred within the first 24 hours post-PCI**

| Time from Balloon Deflation to Onset of CHF | Placebo (N=60) | Bendavia (N=58) | p-value |
|---|---|---|---|
| 0 to 24 hours, % (n) | 25% (15) | 13.8% (8) | 0.16 |
| ≤ *8 hours*, % (n) | 18.3% (11) | 8.6% (5) | 0.18 |
| > *8 to 24 hours*, % (n) | 6.7% (4) | 5.2% (3) | NS |

Values provided for primary analysis population

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# Congestive Heart Failure Within 24 Hours Post PCI

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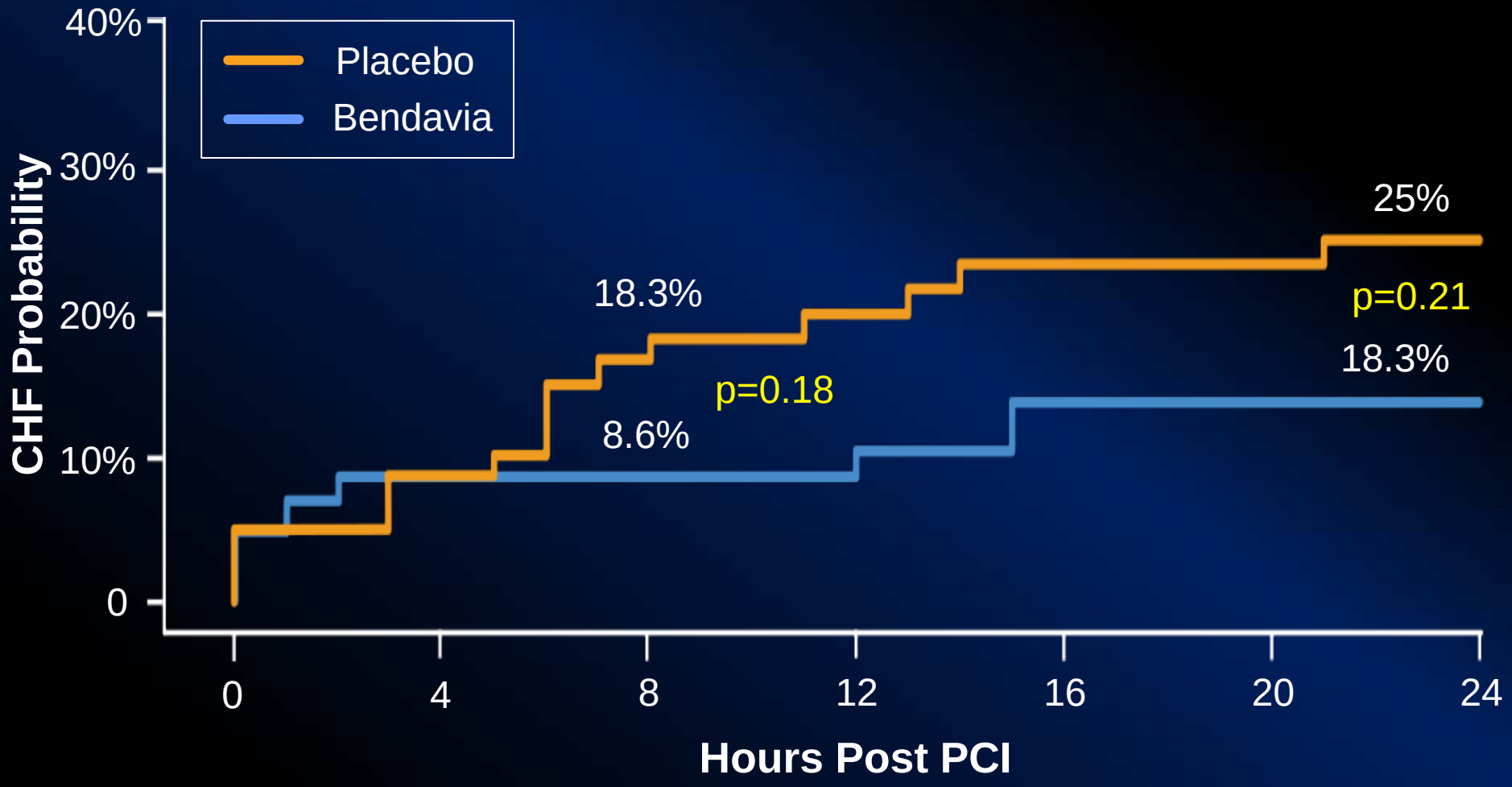


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Values provided for primary analysis population.
P-values based upon Fisher's exact test at respective time points. p-value for KM estimate = NS.

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# Significant Imbalance in Hypertension Between Treatment Arms

Because of the imbalance in the history of hypertension between the two treatment arms (60% in placebo vs. 37.9% in Bendavia, p=0.02), the subgroup of hypertensive patients were evaluated in a non-prespecified exploratory analysis

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# Results: Infarct & Edema Volumes Day 4 Post-PCI

| | Placebo | Bendavia | p-value | p interaction |
|---|---|---|---|---|
| **Infarct Volume at 4 ± 1 Days Post-PCI** | | | | |
| Hypertensive | 52.6 ± 30.2 (N=33) | 35.8 ± 22.8 (N=17) | 0.03 | 0.14 |
| Non-hypertensive | 41.7 ± 23.0 (N=21) | 46.8 ± 23.1 (N=34) | 0.43 | |
| **Edema Volume at 4 ± 1 Days Post-PCI** | | | | |
| Hypertensive | 61 ± 21 (N=34) | 49 ± 22 (N=19) | 0.053 | 0.21 |
| Non-hypertensive | 53 ± 25 (N=21) | 58 ± 28 (N=34) | 0.51 | |

Values provided for primary analysis population

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# ST-Segment Resolution at 24h Post PCI Among Hypertensive Subjects

Preliminary

| | Placebo (N= 34) | Bendavia (N= 21) | p-value |
|---|---|---|---|
| Absent (<30%) | 11.8% (4) | 0.0% (0) | 0.05 |
| Partial (30-70%) | 44.1% (15) | 33.3% (7) | |
| Complete (≥70%) | 44.1% (15) | 66.7% (14) | |

Values provided for primary analysis population

Among hypertensive patients, there was no difference in CK-MB $AUC_{(0\text{-}72)}$ between Bendavia and placebo.

# Results: Treatment Emergent Adverse Events (TEAEs)

Preliminary

| | Placebo (N= 147) | Bendavia (N= 150) | p-value |
|---|---|---|---|
| All-cause death, % (n) | 2.0% (3) | 6.7% (10) | NS |
| *Cardiovascular death, % **(n)*** | 2.0% (3) | 4.0% (6) | |
| *Non-cardiovascular death, % **(n)*** | 0 | 2.7% (4) | |
| Serious TEAE, % **(n)** | 9.5% (14) | 13.3% (20) | |
| New MI**, % (n)** | 4.1% (6) | 1.3% (2) | |
| Congestive heart failure**, % (n)** | 27.9% (41) | 24.7% (37) | |
| Cardiogenic shock**, % (n)** | 0 | 2.7% (4) | |
| Ventricular tachycardia/fibrillation**, % (n)** | 3.4% (5) | 3.3% (5) | |
| AV block**, % (n)** | 0.7% (1) | 0.7% (1) | |
| Stroke / TIA**, % (n)** | 1.4% (2) | 2.7% (4) | |
| Malignancy**, % (n)** | 1.4% (2) | 1.3% (2) | |
| Hyponatremia**, % (n)** | 1.4% (2) | 2.0% (3) | |
| Skin Allergy**, % (n)** | 0.7% (1) | 1.3% (2) | |

Values provided for the safety population.
TEAE are defined as adverse events that are recorded with an onset date and time on or after the date and time of study drug administration through 6 months. The causes of the 4 non-cardiovascular deaths include cancer, rhabdomyolysis, gastrointestinal bleeding, and septic shock and all occurred 49 days or more following drug infusion.

# Safety: Creatinine

Exploratory analyses:

Bendavia was associated with a significantly lower change in Cr over the first 12 hrs (1.0 vs 3.7 µmol/li, p=0.03)

Over the first 48 hrs after PCI, the AUC for Cr was lower for Bendavia (3519.1 $\pm$ 90.4 µmol hrs /li, n=148) vs placebo (3732.0 $\pm$ 90.3 µmol hrs/li, n=145, univariate p=0.10, multivariate p=0.04 adjusting for baseline Cr & duration of PCI procedure, a surrogate for dye load).

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# Summary

Bendavia did not reduce the primary endpoint of infarct size by CK-MB $AUC_{(0\text{-}72h)}$

There was a significant imbalance in hypertension (60% vs 37.9%, p=0.02), and in a non-prespecified analysis of hypertensive patients, Bendavia significantly reduced day 4 MRI infarct size (35.8 mL vs. 52.6 mL, p=0.03) & improved ST resolution (p=0.05)

During the 8 hours during / following Bendavia administration, there was a trend towards reduced symptomatic heart failure (8.6% vs. 18.3%, p=0.18)

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# Conclusion

Among patients with a first anterior ST-elevation MI due to a proximal or mid LAD occlusion who undergo successful PCI

Bendavia administered at a dose of 0.05 mg/kg/hr for 1 hour was safe and well tolerated & did not significantly reduce CK-MB area under the curve

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# Future Directions

The hypothesis generating data that demonstrated a trend toward a favorable reduction in CHF symptoms in the 8 hours during / following Bendavia administration is being prospectively evaluated at comparable and higher doses in an ongoing trials of patients with systolic heart failure (HFREF) (NCT02388464 & NCT02388529) and renal protective effects in trial NCT01755858

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