PRESERVATION I

A placebo-controlled, multicenter, randomized, double-blind trial to evaluate the safety and effectiveness of IK-5001 (Bioabsorbable Cardiac Matrix [BCM]) for the prevention of remodeling of the ventricle and congestive heart failure after acute myocardial infarction

ClinicalTrials.gov Identifier: NCT01226563

Uwe Zeymer, Sunil V. Rao, Mitchell W. Krucoff,
on behalf of the PRESERVATION I Investigators

Klinikum Ludwigshafen, Germany,
and Duke Clinical Research Institute, Durham, NC, USA

Duke Clinical Research Institute

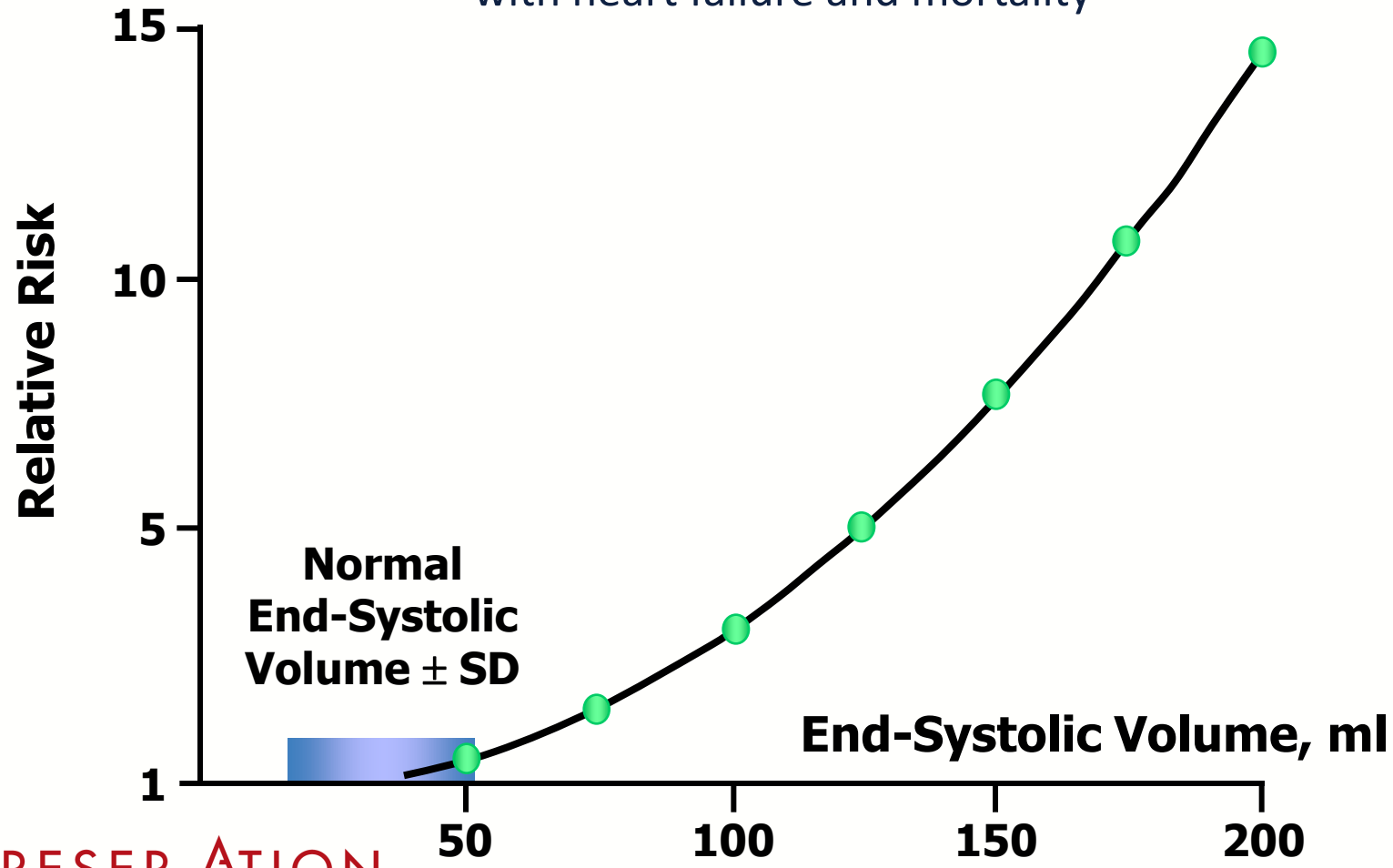
Bellerophon THERAPEUTICS

Disclosure

- U.Z. has received honoraria
- S.V.K and M.W.K. have received compensation for their participation as members of the Executive Committee of the PRESERVATION I trial

BACKGROUND

Pathologic ventricular remodeling after large MI impairs left ventricular (LV) function and is associated with heart failure and mortality



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White et al. *Circulation*. 1987;76:44

Device: Bioabsorbable Cardiac Matrix (IK-5001)

- Large infarcts are associated with the degradation of extracellular matrix (ECM) and calcium overload
- BCM is a combination of 1% Na^+ alginate with 0.3% Ca+ gluconate in water, it is biologically and immunologically inert, and does not undergo metabolism
- In the presence of free calcium BCM turns to flexible hydrogel
- The gel replaces the degraded ECM, thickening the infarct zone and reducing wall stress
- BCM provides mechanical support and prevents consistently remodeling in several animal models and a human pilot study

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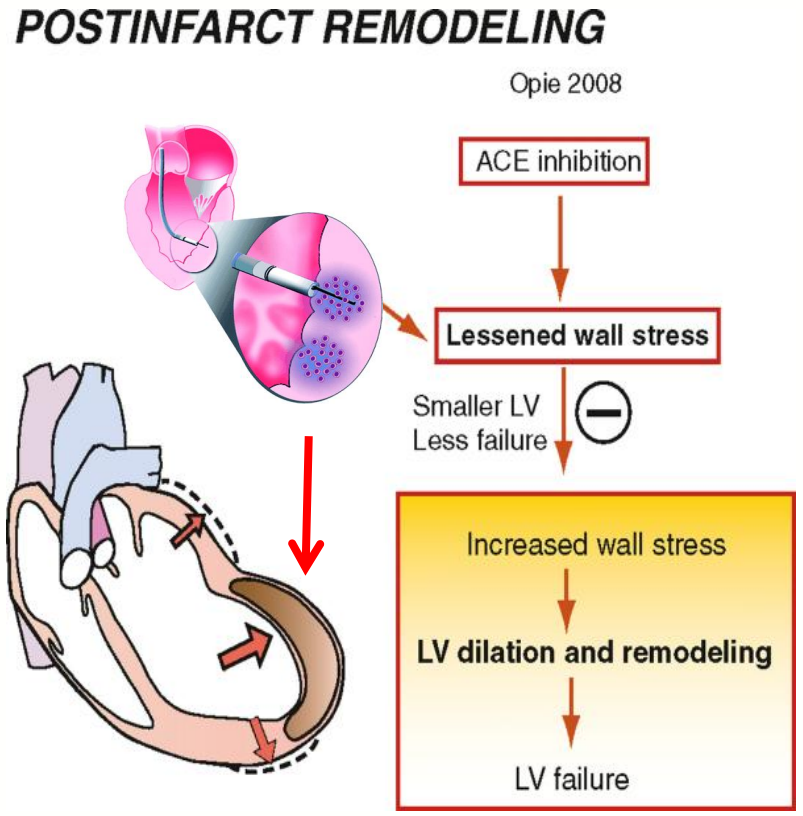
Trial hypothesis

- Can the intracoronary deployment of an inert bioabsorbable cardiac matrix replace the damaged extracellular matrix and provide a temporary physical support during infarct healing and repair and prevent remodeling ?



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Trial Organization

- Steering committee
  - Mitchell Krucoff (study chair), Sunil Rao (co-PI), Uwe Zeymer (co-PI)
  - Pamela Douglas, Norbert Frey, Jaroslav Kasprzak, Paul Vermeersch, Jerome Roncalli, José López-Sendón, Victor Guetta, Henry Krum, Derek Chew, Jean-François Tanguay, Tim Henry, Hussein Al-Khalidi, Howard Levy, Reinilde Heyrman
- Coordinating Center: DCRI
- Data safety monitoring board: Chaired by Magnus Ohman (DCRI)
- Event Adjudication Committee (DCRI)
- Core laboratories for
  - Echocardiography (DCRI, Pamela Douglas)
  - 24-hour Holter & ECG (DCRI, Mitchell Krucoff)
  - Deployment angiogram (PERFUSE, Michael C. Gibson)
- Sponsor: Bellerophon Therapeutics

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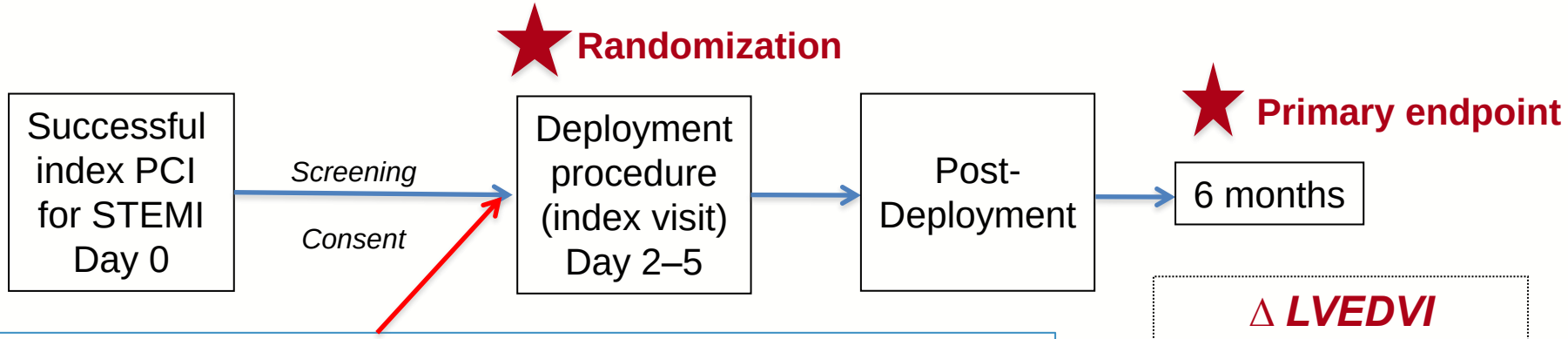
Trial design

Prospective, randomized, double blind trial



- Inclusion criteria:
  - Large STEMI defined by
    - Peak cardiac markers
    - Clinical presentation (delayed PCI, ECG, shock)
    - Imaging (EF≤ 35% or MI size > 20%)
- Exclusion criteria: cardiogenic shock during planned deployment, ventricular arrhythmias, renal insufficiency, inadequate echo images

Δ LVEDVI

Echo (2 & 3D)

Δ KCCQ / SF-12

Δ 6MWT

Δ NYHA class

Δ NT-Pro-BNP

ECG

Clinical outcomes

AEs/SAEs

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Endpoints

Primary endpoint:

- Change in LV end diastolic volume index (LVEDVI) from baseline to 6 months
  - 80% power with 276 pairs to detect a difference of 5 mL/m^2 based on a standard deviation of 13.89 mL/m^2, $\alpha = 0.05$
- 3D echocardiographic assessment of LV dilation
  - Accuracy and reproducibility equivalent to cardiac magnetic resonance imaging
  - Readily available in most centers and easily accepted by patients

Secondary endpoints:

- Kansas City Cardiomyopathy Questionnaire (KCCQ)
- Six-minute walk test (6MWT)
- New York Heart Association (NYHA) functional classification
- Time to death or non-fatal heart failure events or cardiovascular hospitalizations adjudicated by a clinical events committee
- Time to first rehospitalization due to any cardiovascular event

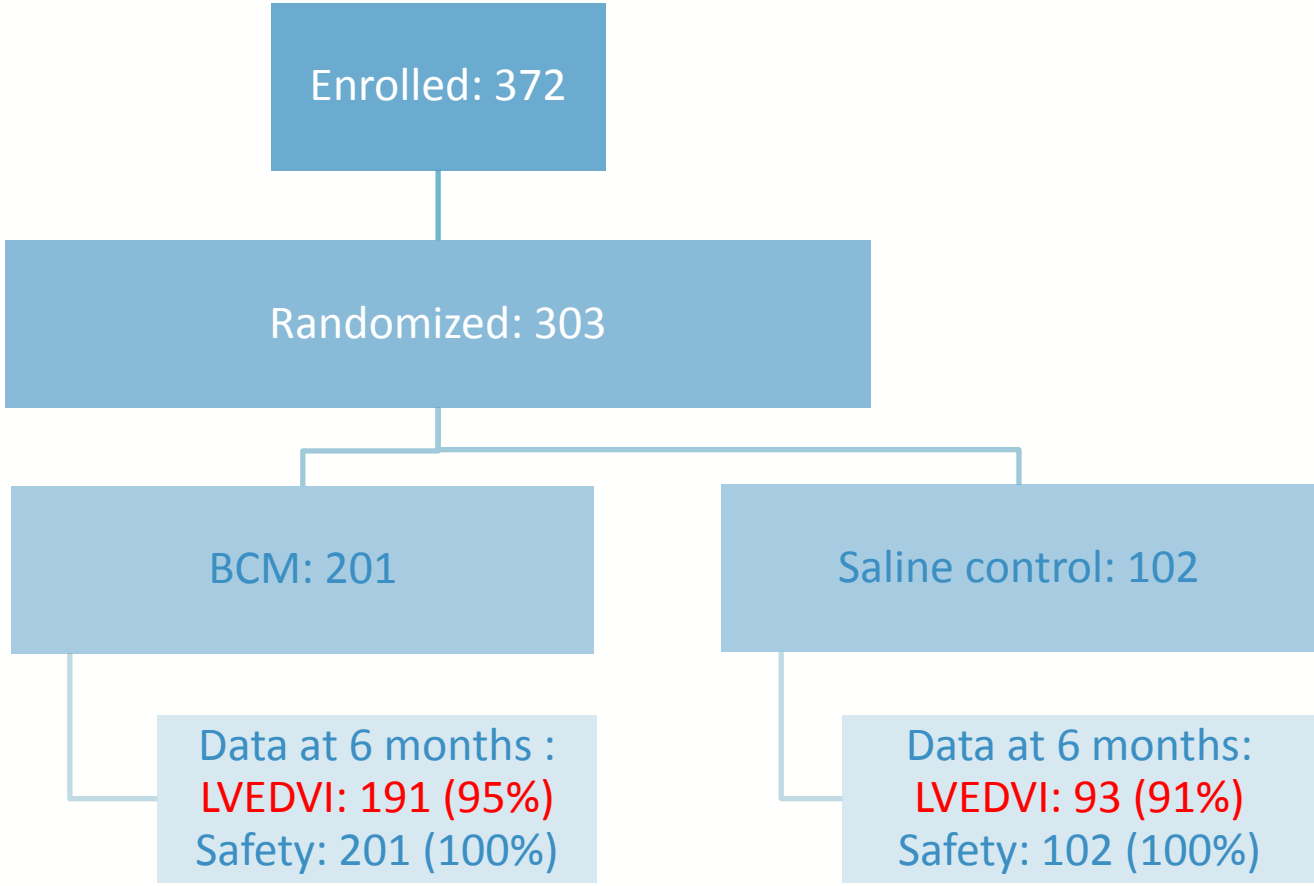
Deployment procedure

- Patients had to have TIMI 3 flow before injection
- An intracoronary injection of 4 mL BCM or saline control (sham procedure) in a second procedure 2–5 days after primary PCI was performed
- The deployment was performed via a dedicated catheter proximal to the stent of the infarct-related artery

CONSORT diagram

Enrolment in 64 centers in 9 countries between 04/2012-12/2014

Screen failure reasons	
Did not meet inclusion criteria	27
Met exclusion criteria	6
No TIMI 3 flow at protocol-specified catheterization	5
Death	3
Other	28



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Baseline characteristics

	BCM N=201	Saline control N=102
Age	58.4 ± 10.84	57.6 ± 10.75
Male	82.1%	80.4%
Diabetes	18.9%	15.7%
Anterior MI	93.0%	92.2%
LVEF	33.9 ± 6.40	35.4 ± 7.13
Infarct size (CMR or SPECT)	(n=40) 36.0 ±14.14	(n=25) 29.4 ± 9.73
NT-pro-BNP	499.9 ± 562.94	376.1 ± 399.82
End-diastolic volume index	84.8 ± 16.21	82.1 ± 14.74

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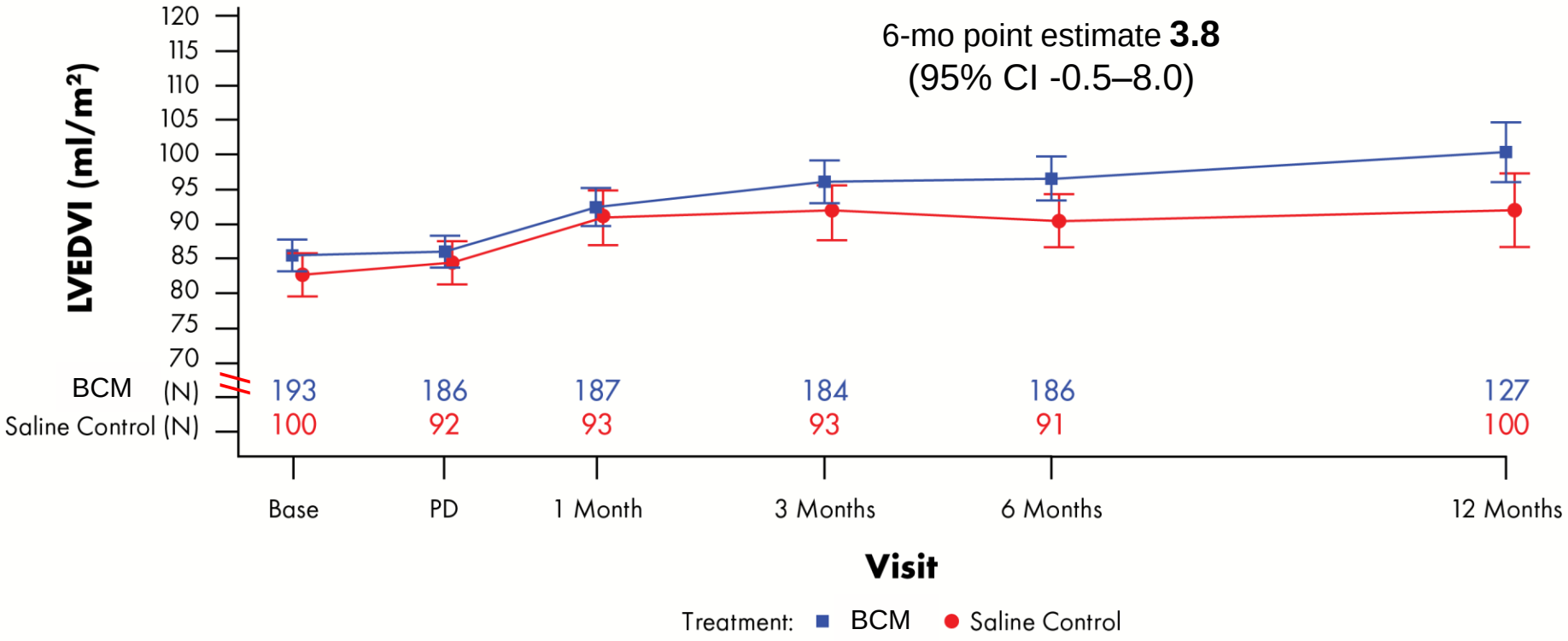
Medical treatment at discharge

	BCM	Saline control
Statin	79.1%	86.3%
Beta-blocker	86.6%	86.3%
ACE-I	79.6%	81.4%
ARB	12.9%	7.8%
Mineralocorticoid antagonist	30.8%	32.4%

Primary endpoint: LVEDVI



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Change from baseline at 6 months for secondary endpoints

Parameter	BCM Mean ± SD	Saline control Mean ± SD	Point estimate (95% CI)	P value
ΔKCCQ	0.5 ± 22.65	0.8 ± 26.80	0.3 (-5.9–6.4)	0.931
Δ6MWT, min	135.6 ± 146.13	101.4 ± 139.22	34.3 (-0.2–68.7)	0.051
NYHA improvement	25.1%	22.8%		0.623
NYHA worsening	20.1%	21.8%		
CV hospitalization	14.7%	10.2%		0.143
Death	2.0%	2.9%		n.s.
Number of deaths, non-fatal CHF, CV hospitalization	15.6%	11.2%		0.153

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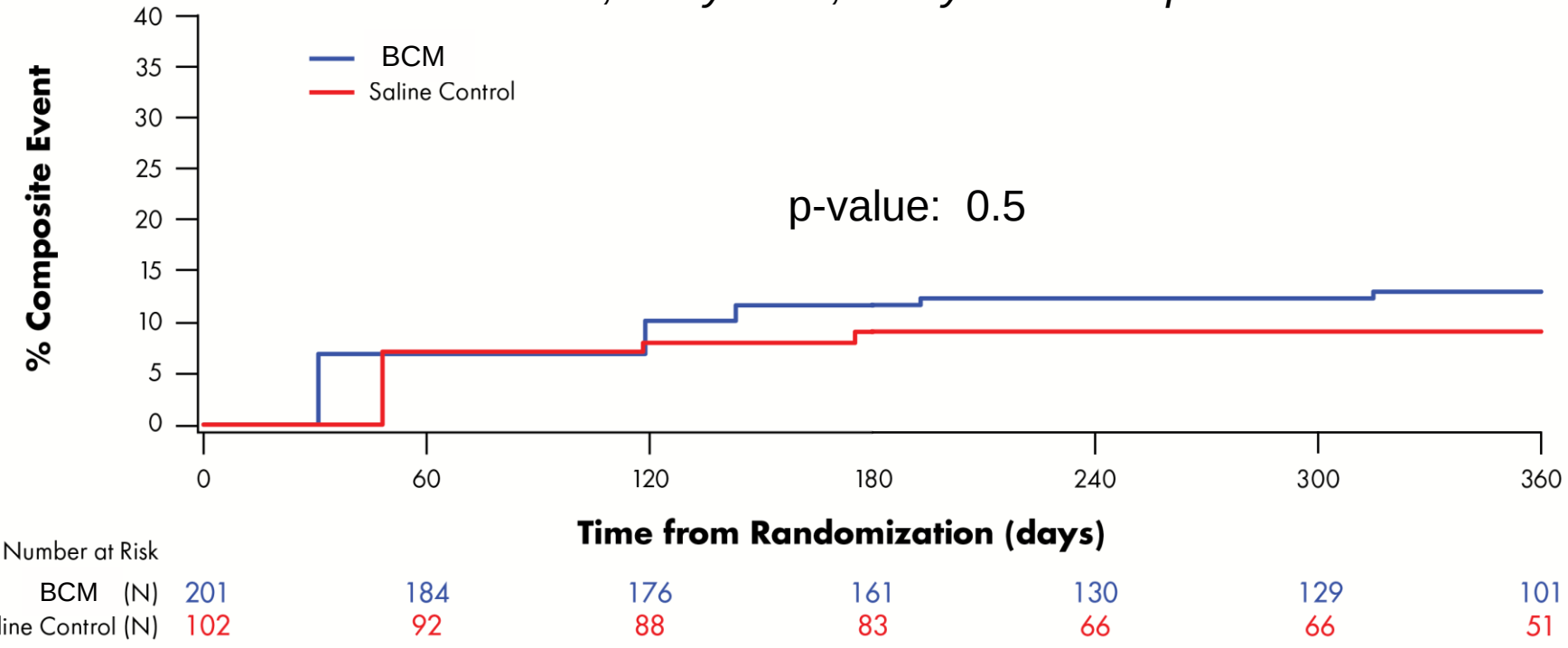
Safety parameters

Kaplan-Meier of composite of CV death, acute MI, revascularization, stent thrombosis, arrhythmia, or myocardial rupture



Number at Risk							
BCM (N)	201	184	176	161	130	129	101
Saline Control (N)	102	92	88	83	66	66	51

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Procedural safety

- Repeat catheterization
  - 22% had staged PCI scheduled
- No difference between BCM and saline

  - arrhythmias on 24-hour Holter

  - ischemia: BCM 9% - Saline 7.8%,
- Angiographic assessment coronary artery flow
  - 5 occlusions in BCM (but only 3 also ischemia on Holter)
  - 1 occlusion in saline control

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Conclusions

- Able to identify and enroll large STEMI patients
  - BCM deployed 2–5 days after primary PCI was well tolerated compared to saline control
  - The additional invasive procedure carries risks, albeit minimal
- In patients with large STEMI, intracoronary BCM does not prevent LV remodeling compared to saline control nor the occurrence of heart failure
  - Secondary endpoints (NYHA class, functional capacity) did not show clinical difference between BCM and saline control

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Discussion

- Reason for discrepant findings compared to animal data ?

- Future direction:
  - Different patient population ?
  - Different timing of deployment ?
  - Device deployment technology ?
  - Combination with stem cells ?

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Investigator enrollment

With our sincere thanks to all participating patients

Name	#	Name	#	Name	#	Name	#	Name	#
Vermeersch	**23**	Turgeman	9	Chew	4	Teiger	2	Van Belle	1
Zeymer	**21**	Abbott	9	Rosenschein	4	Krum	2	Fernandez	1
Garrahy	14	Guetta	8	López-Sendon	4	Chorianopoulos	2	Erickson	1
Kracoff	13	Frey	8	Behrens	4	Vanzetto	2	Greenbaum	1
Traverse	13	Roncalli	7	Kokis	3	Wysokinski	2	Yakubov	1
van Gaal	12	Horowitz	7	Waksman	3	Abergel	2	Elsässer	1
Pollak	10	Bruguera	7	Jayasinghe	3	Bortnick	2	Logeart	1
Brass	10	Kasprzak	6	Katz	3	Gilchrist	2	Bosle	1
Zamorano	10	Sarembock	6	Cawthon	3	Lasorda	2	Buller	1
		Figulla	6	Gruberg	3	Daggubati	2	Cantor	1
		Schoors	6	Legrand	3	Lehmann	2	Ohlman	1
		Nguyen	6	Dens	3	Lapp	2		
		Tanguay	6	Quraishi	3	Rozenman	2		
				Tiroch	3				
				Juanatey	3				

Statistical analysis by DCRI :
Hussein Al-Khalidi & Jennifer White

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With thanks to CROs:

- DCRI in NA (Diane Joseph)
- WCT in ROW (Helen Treece)