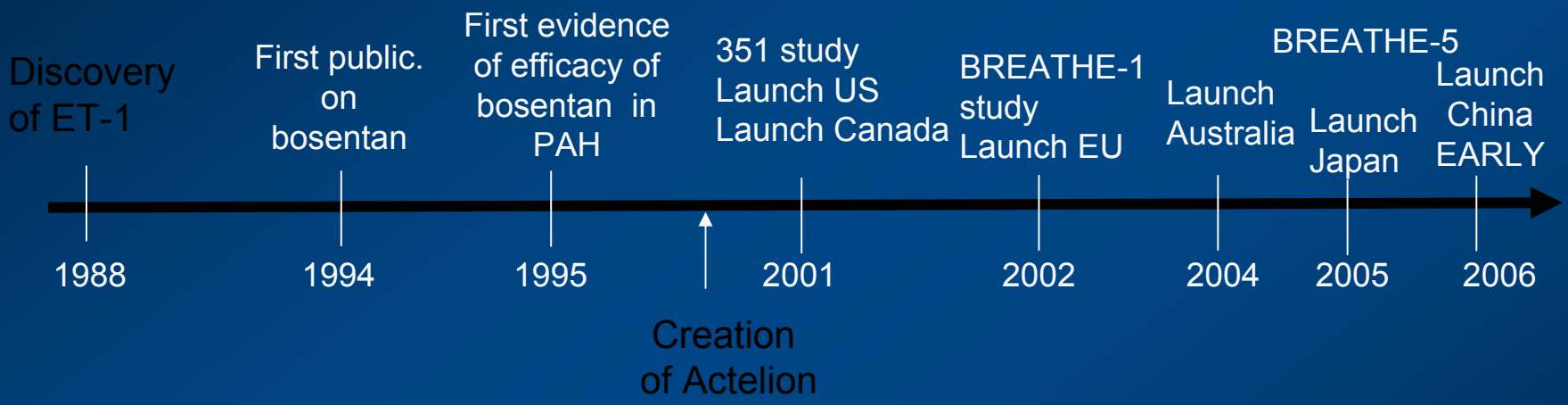
Development of Tracleer® (bosentan)



18 years' research in ET and ET receptor antagonists,

more than 130 manuscripts published by our group

Bosentan (Tracleer®)
Oral dual ET receptor antagonist

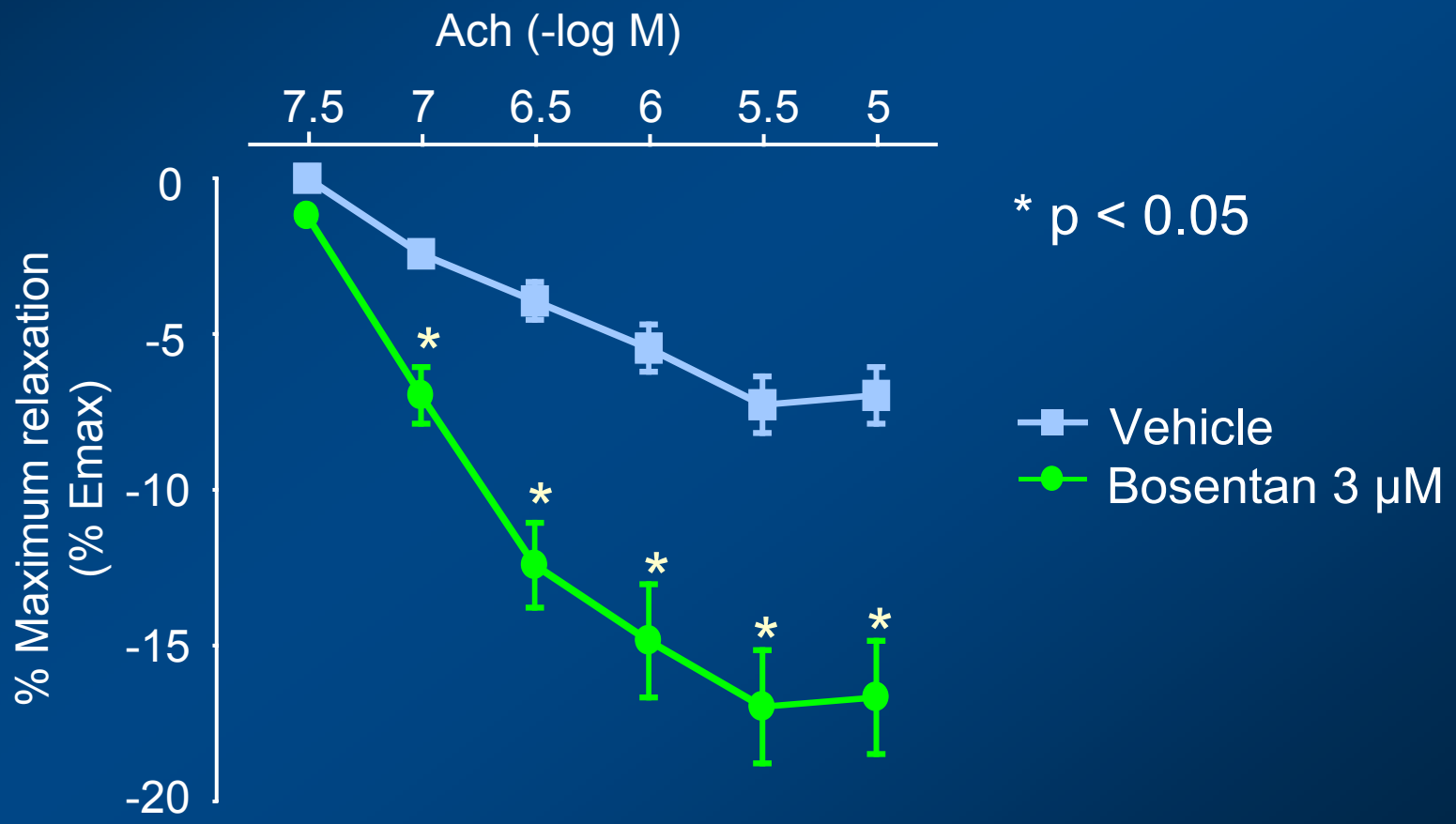
Roux et al. J Mol Med 1999;77:364

Main pharmacological properties of bosentan

- Vasodilation
- Anti-hypertrophic
- Anti-fibrotic
- Anti-inflammatory

Dumont et al. 2001; Chen et al. 1995; Park et al. 1997; Finsnes et al. 1997

Bosentan induces vasodilation

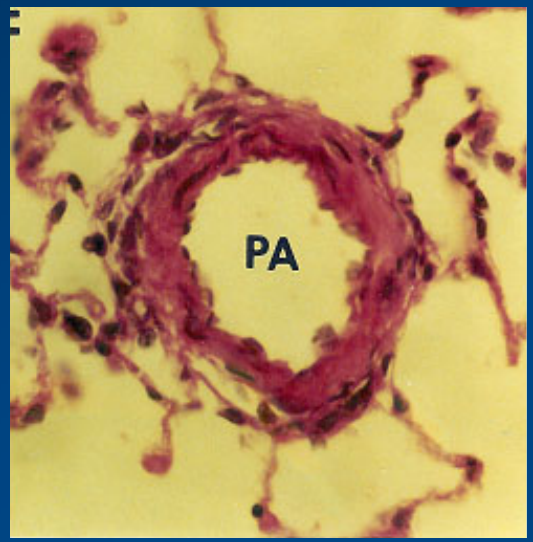


In vitro model: Human saphenous veins pre-contracted with phenylephrine

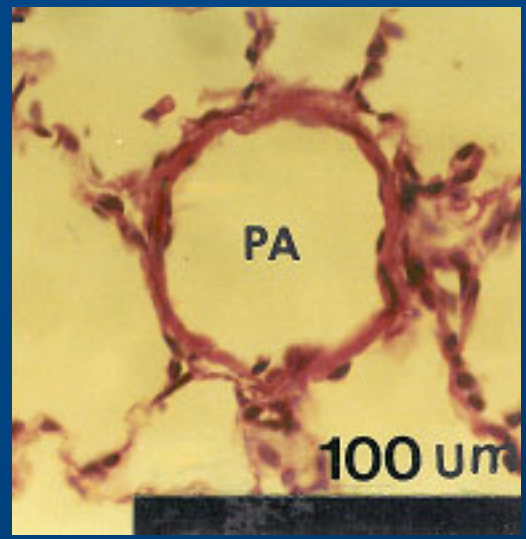
Dumont et al. J Neurosurg. 2001;94:281

Bosentan prevents and reverses vascular hypertrophy

Significant reduction in pulmonary arterial wall thickness vs. control (*p* <0.01)



6 wks hypoxia
+ 4 wks placebo



6 wks hypoxia
+ 4 wks bosentan

Rat hypoxic model of pulmonary hypertension

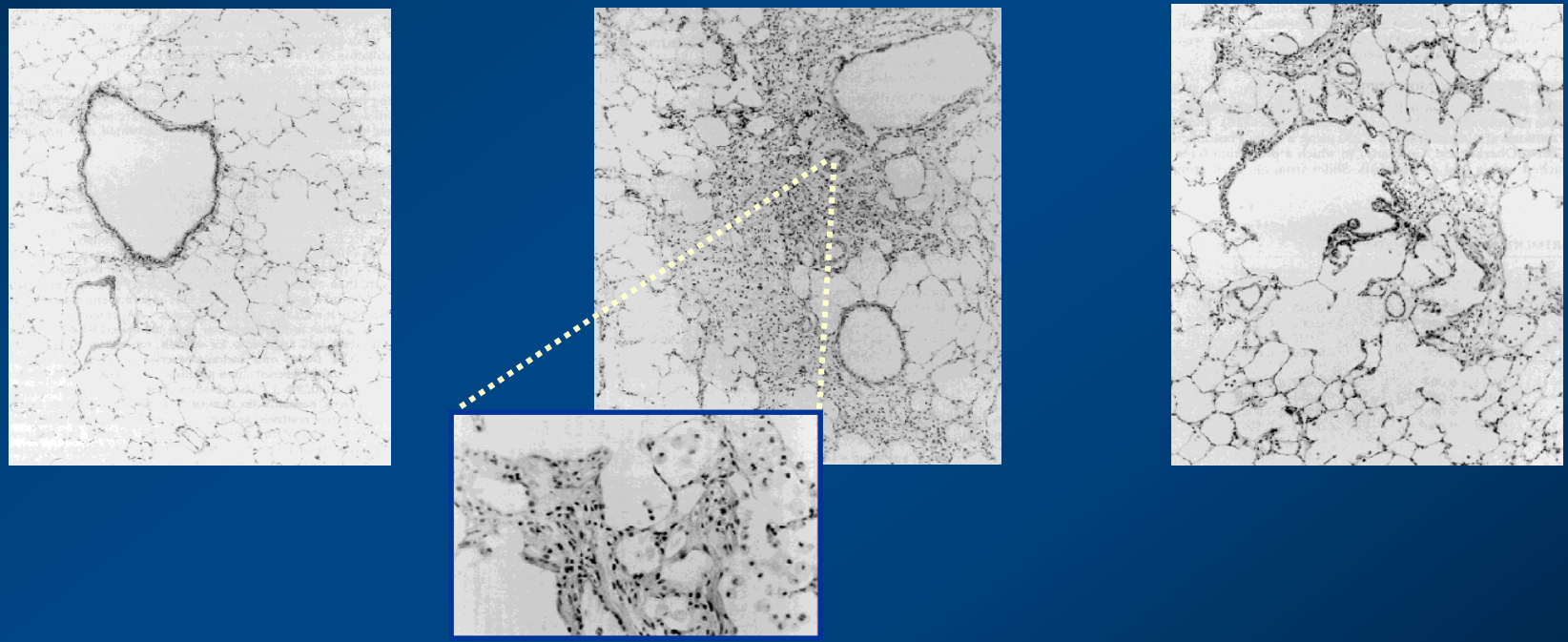
Chen et al. J Appl Physiol 1995;79:2122

Bosentan attenuates pulmonary fibrosis

Control

Bleomycin

Bleomycin + Bosentan

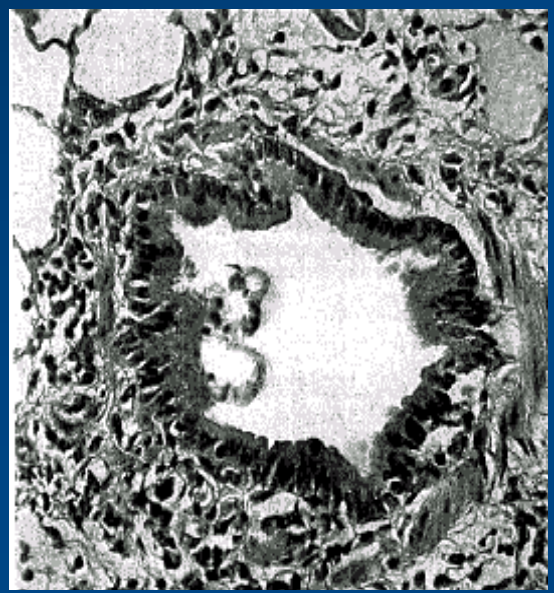


Rat model of bleomycin-induced fibrosis

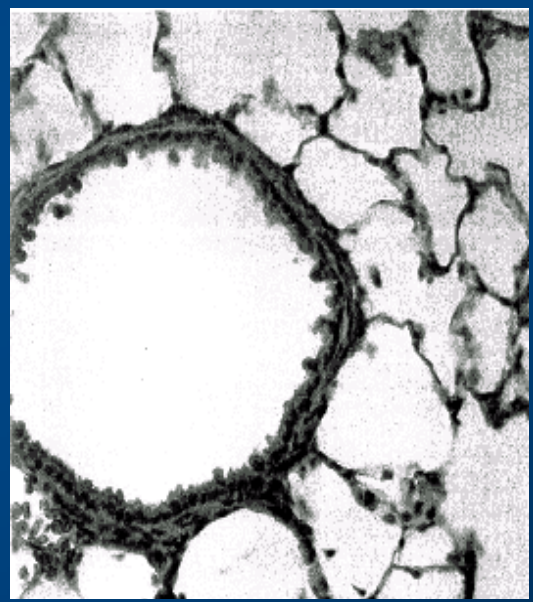
Park et al. Am J Respir Crit Care Med 1997;156:600

Bosentan reduces inflammation

Sephadex (Control)



Sephadex + Bosentan



Rat model of sephadex-induced peribronchial inflammation

Finsnes et al. Am J Respir Crit Care Med 1997;155:1404

Bosentan Was Tested and Showed Efficacy in Animals Models of:

- Hypertension
- Acute renal failure
- Chronic renal failure
- Pulmonary hypertension
- Heart Failure
- Subarachnoid hemorrhage
- Migraine
- Cancer
- Stroke
- Septic shock
- Gastric ulcus
- Inflammatory Bowel Disease
- Diabetes
- Organ transplant
- Cirrhosis
- Pulmonary fibrosis

Bosentan pharmacokinetics

Absorption and distribution

- Orally active
  - Bioavailability 50%, no food effect
- Highly protein bound (98%)

Elimination (half life 5.4 hours)

- Hepatic metabolism
  - Cytochrome P450 (CYP) 3A4 and CYP2C9
    3 metabolites – 1 pharmacologically active
- Biliary excretion
  - < 6% in urine (parent + metabolites)

Prakash et al. Am J Cardiovasc Drugs 2002,2:335

Bosentan pharmacokinetics

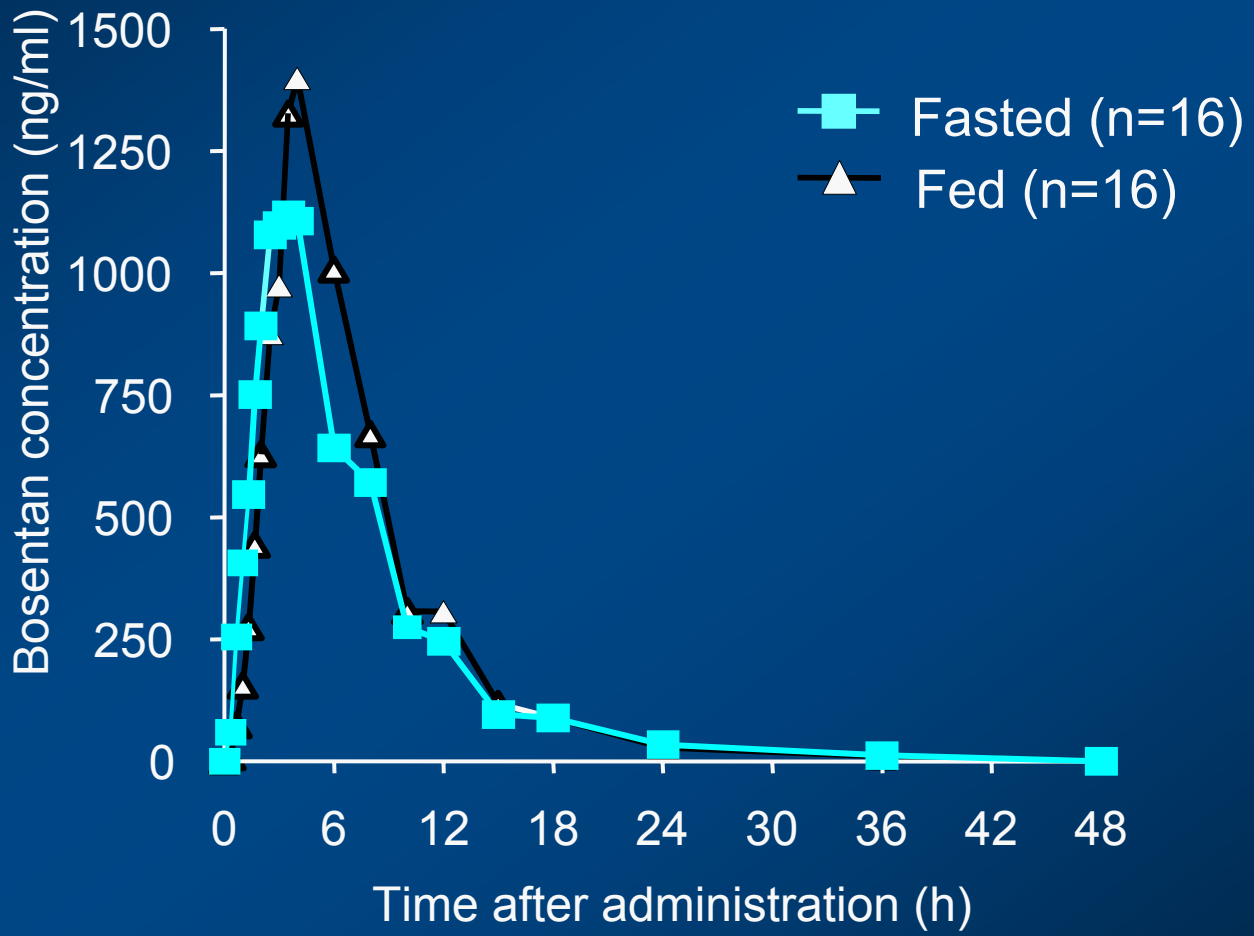
PK parameters following bosentan 125 mg

C_{max}	1.3 µg/mL (1.1-1.6)
t_{max}	3.5h (1.7-8.0)
$t_{1/2}$	5.4 h (4.5-6.4)
$AUC_{0-\infty}$	8.0 µg • h/mL (6.3-10.0)

(n=16 healthy volunteers)

Dingemanse et al. J Clin Pharmacol 2002;42:283

Bosentan PK is unaffected by food



Dingemanse et al. J Clin Pharm 2002;42:283

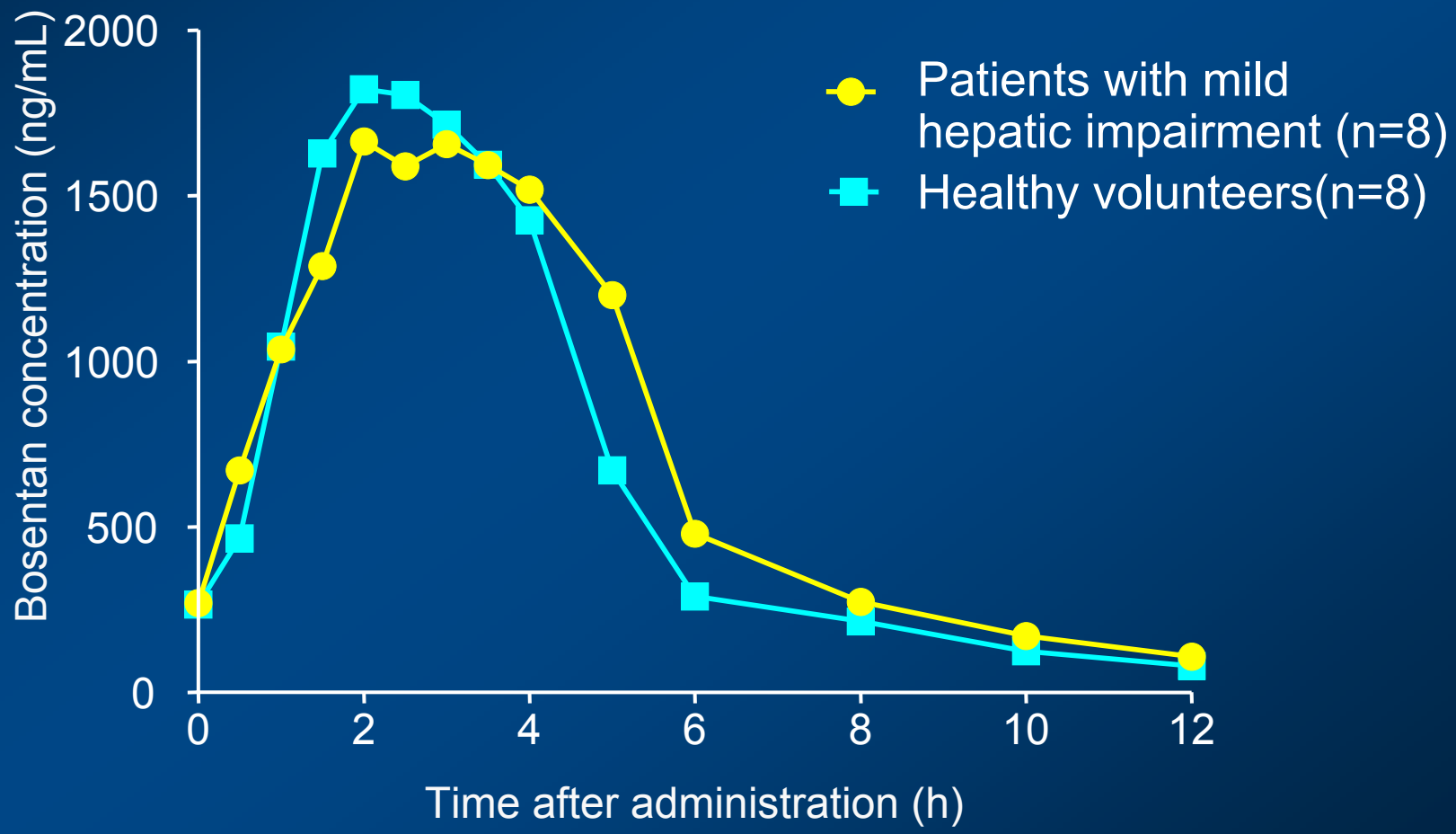
Bosentan dosing in special populations

Elderly (>65 y): No dose adjustment needed

Renal impairment: No dose adjustment needed (also with dialysis)

Hepatic impairment:
Mild: No dose adjustment needed
Moderate / Severe: Contra-indicated

No dose adjustment in mild hepatic impairment



van Giersbergen et al. J Clin Pharmacol 2003;43:15

Bosentan exposure in children with PAH

Multiple dose comparison

	Dose (mg)	AUC_{τ} (ng•h/ml)	C_{max} (ng/ml)
Pediatric patients:			
10 - 20 kg (n=7)	31.25	3496	685
20 - 40 kg (n=6)	62.5	5428	1136
> 40 kg (n=6)	125	6124	1200
Adult patients	125	8149	1878

Barst et al. Clin Pharmacol Ther 2003;73:372

Phase exploratoire

Bosentan a été testé chez l'homme dans les indications suivantes:

Migraine

Hypertension arterielle

Insuffisance cardiaque

Complications des anti-inflammatoires

Hemorrhagie sous arachnoidienne

Hypertension pulmonaire

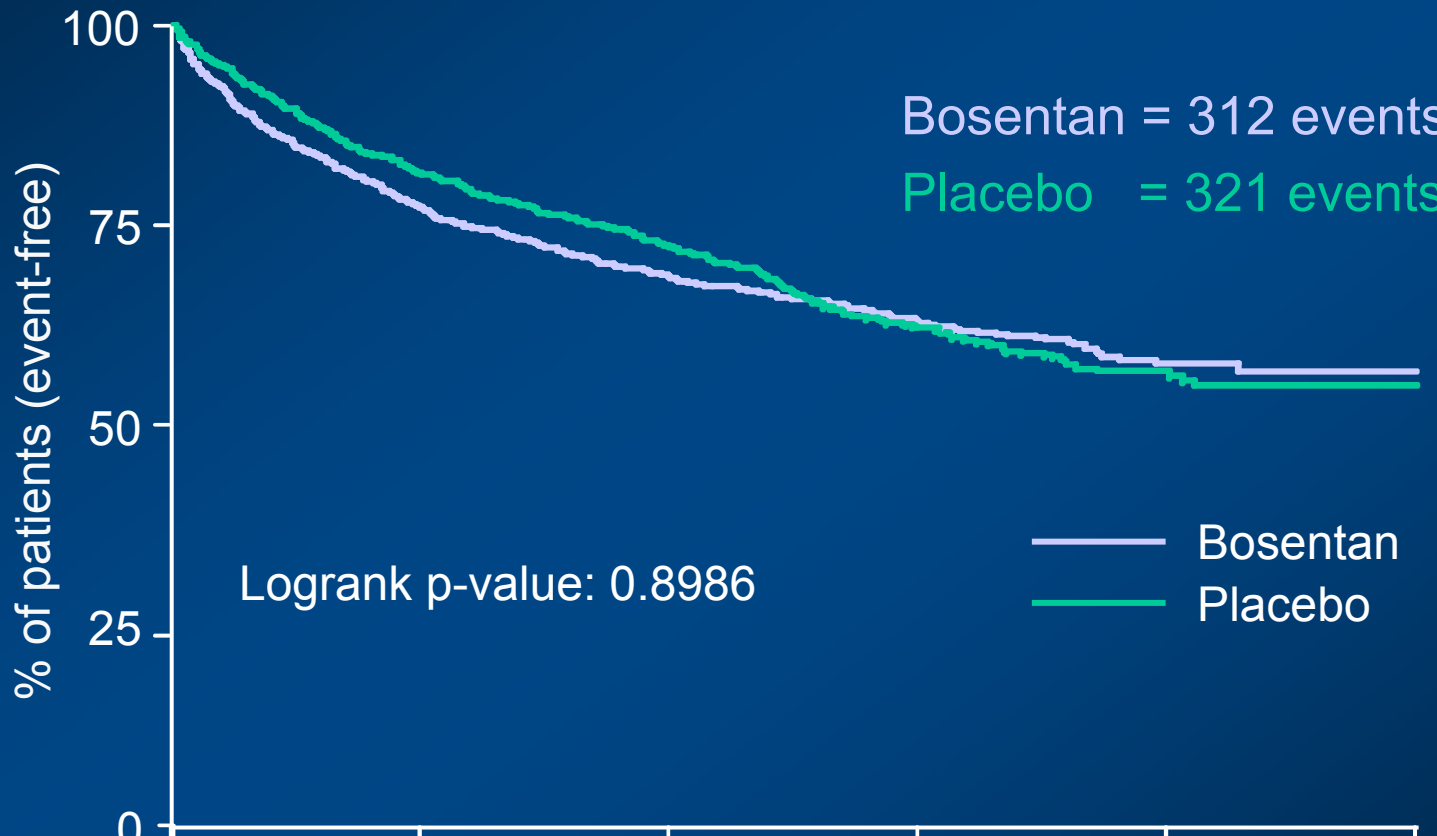
Angioplasties coronariennes

ENABLE-1 / -2: Study design

Mean follow-up = 1.5 years

Actelion: Data on file

ENABLE: Death or CHF hospitalization



Pts at risk						
Bosentan	804	615	542	393	123	0
Placebo	807	655	577	388	113	0

Actelion: Data on file

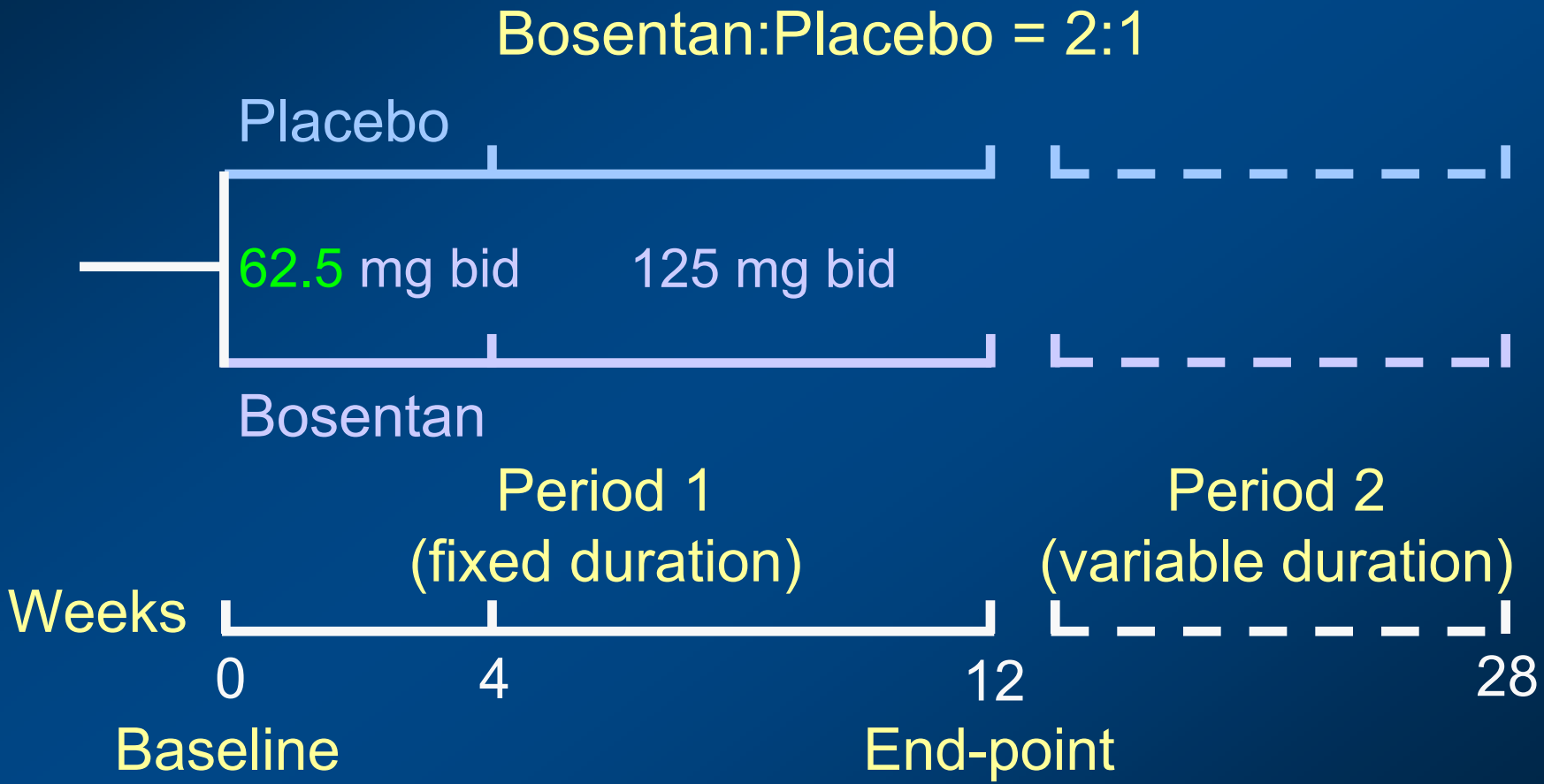
Bosentan, a dual endothelin receptor antagonist improves exercise capacity and hemodynamics in patients with pulmonary arterial hypertension

R. Channick, L. Rubin, G. Simonneau, I. Robbins,
V. Tapson, A. Frost, D. Badesch, F. Bodin, S. Roux

Investigators

D. Badesch	University of Colorado, Denver
R. Channick	University of California, San Diego
A. Frost	Baylor College of Medicine, Houston
I. Robbins	Vanderbilt University, Nashville
L. Rubin	University of California, San Diego
G. Simonneau	Hôpital Antoine Beclere, Paris
V. Tapson	Duke University, Durham

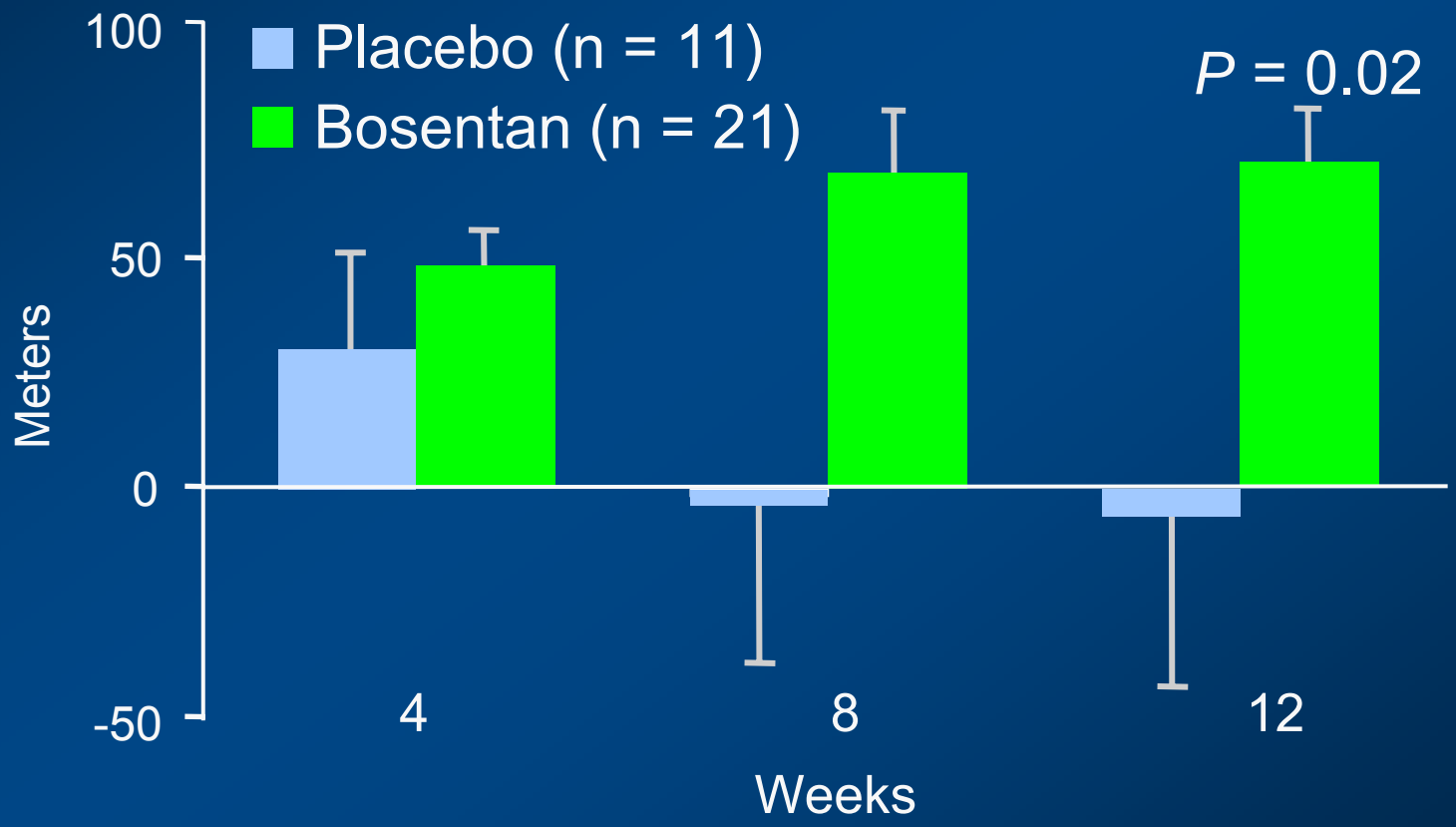
Study design



Channick et al. Lancet 2001;358:1119

6-Minute walk test

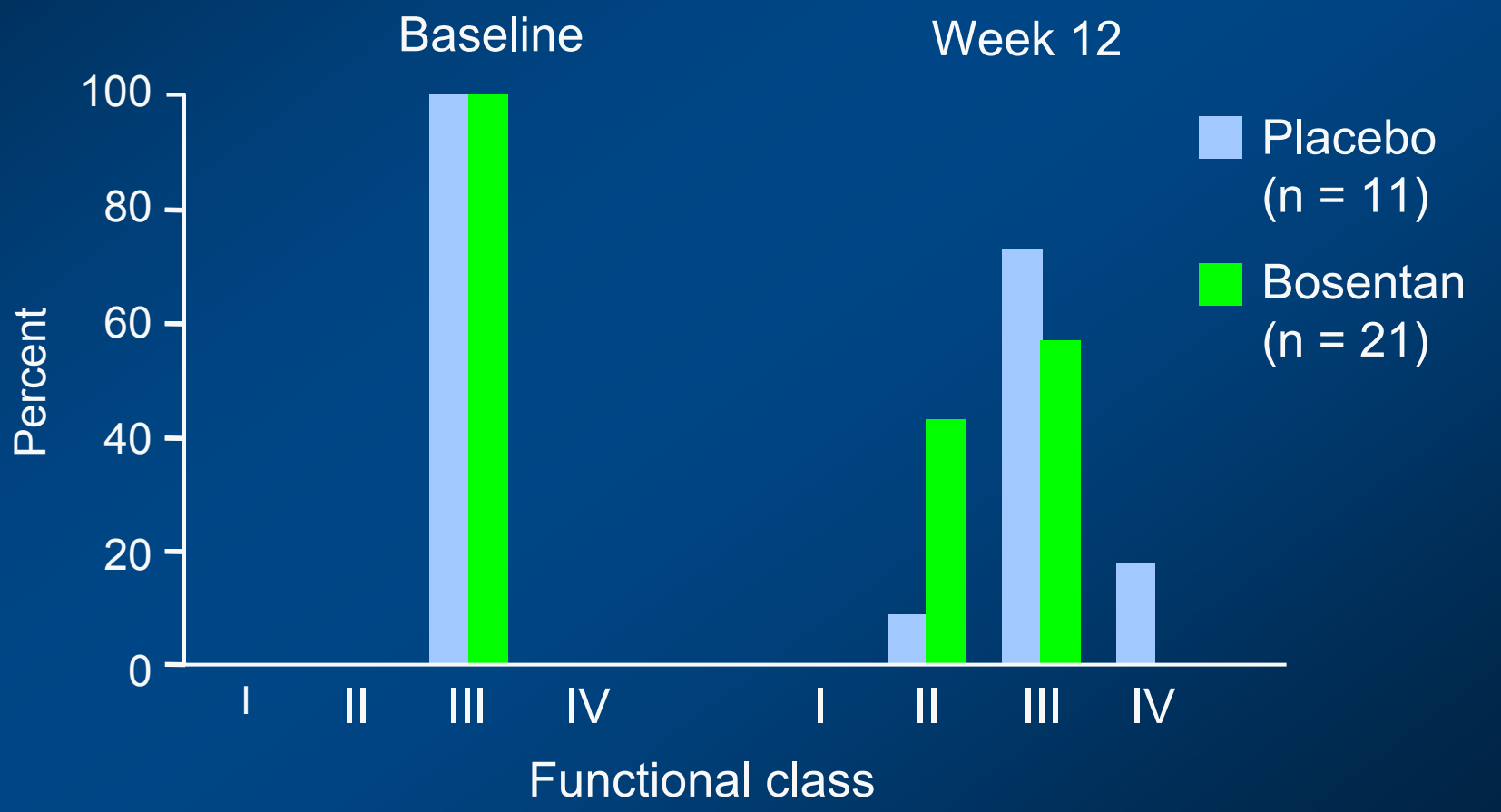
Change from baseline over time



Channick et al. Lancet 2001;358:1119

WHO functional class

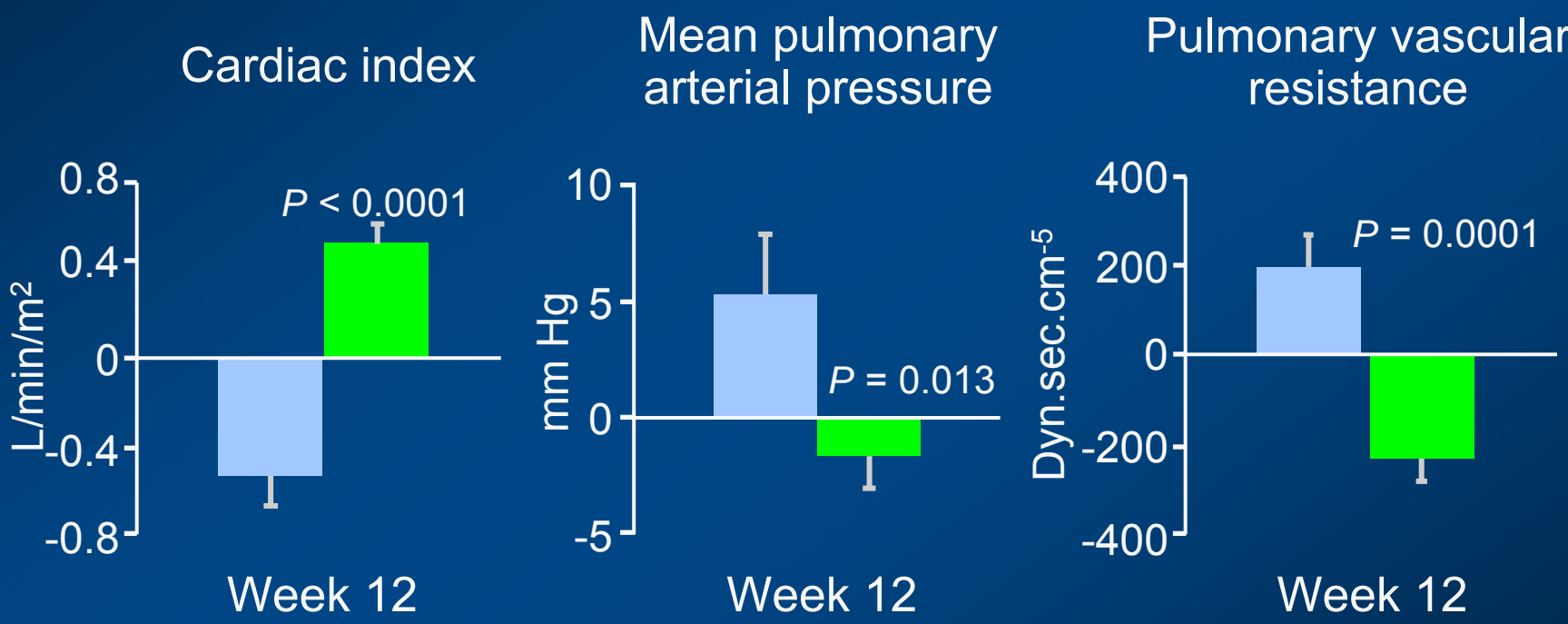
Change from baseline to week 12



Channick et al. Lancet 2001;358:1119

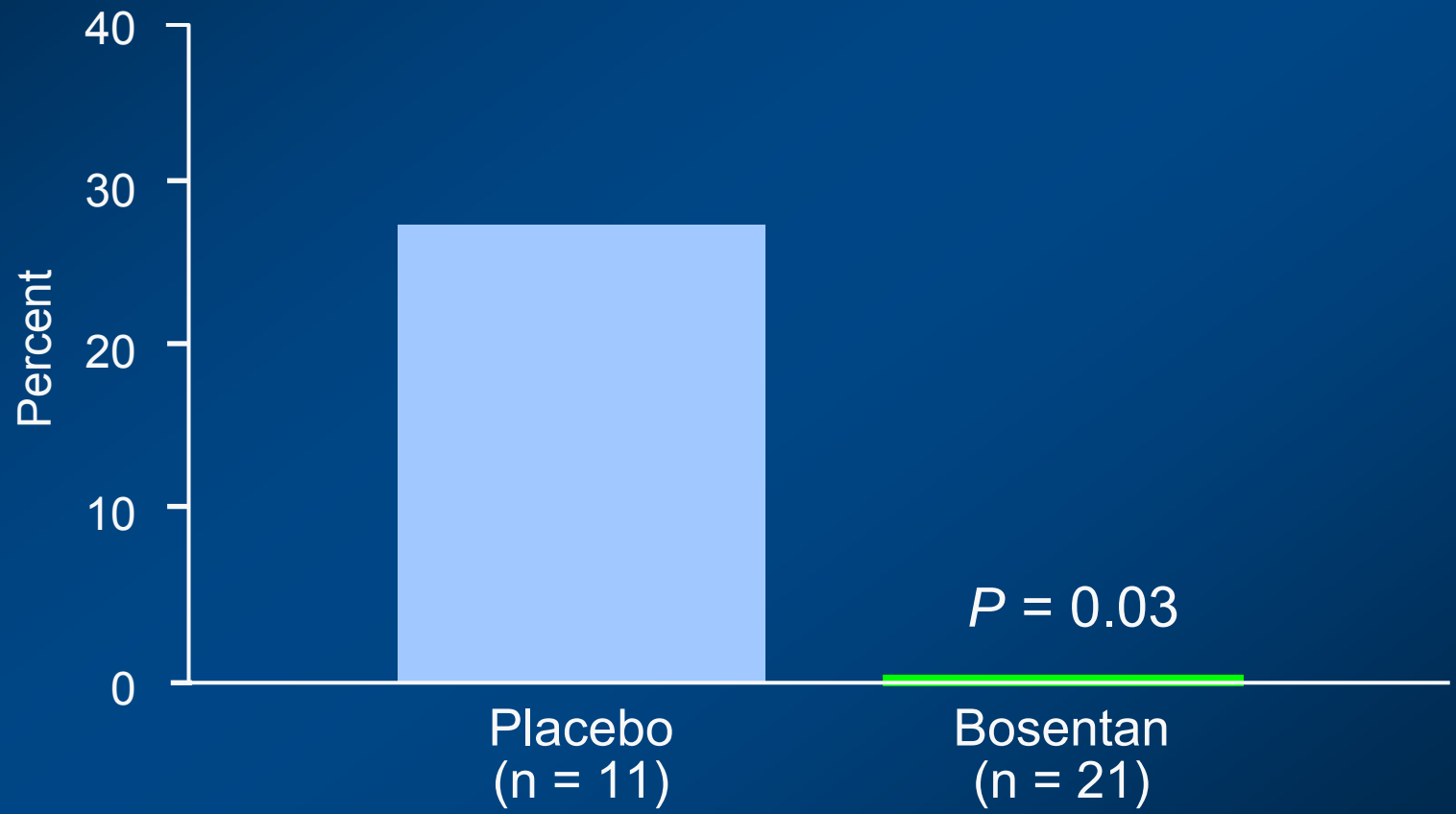
Hemodynamics

Change from baseline to week 12



Channick et al. Lancet 2001;358:1119

Clinical worsening within 28 weeks



Channick et al. Lancet 2001;358:1119

TRACLEER™ (bosentan)

BREATHE-1

BREATHE-1
Bosentan randomized trial of endothelin receptor antagonist therapy for pulmonary hypertension:

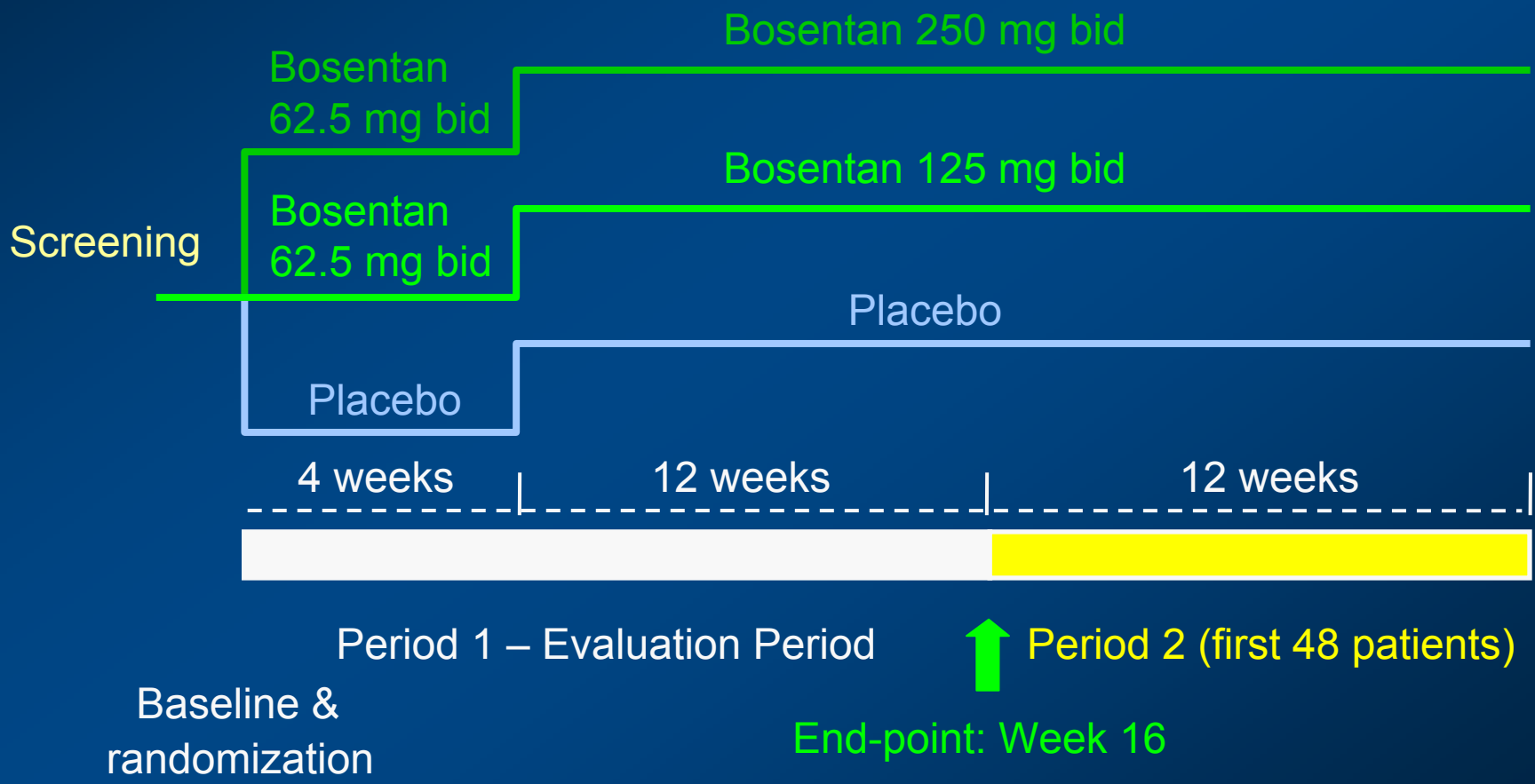
- 11 countries, 27 sites, 213 patients
- Mid-July 2000 to Dec 2000
- Last patient last visit: March 30, 2001

Objectives of BREATHE-1

- To confirm the positive effects of bosentan on exercise capacity in PAH
- To evaluate the effect of bosentan on time to clinical worsening (16 and 24 weeks)
- To explore the dose response of two doses of bosentan on exercise capacity
- To evaluate the safety and tolerability of bosentan

Rubin et al. NEJM 2002;346:896

Study design



Rubin et al. NEJM 2002;346:896

Definition of time to clinical worsening

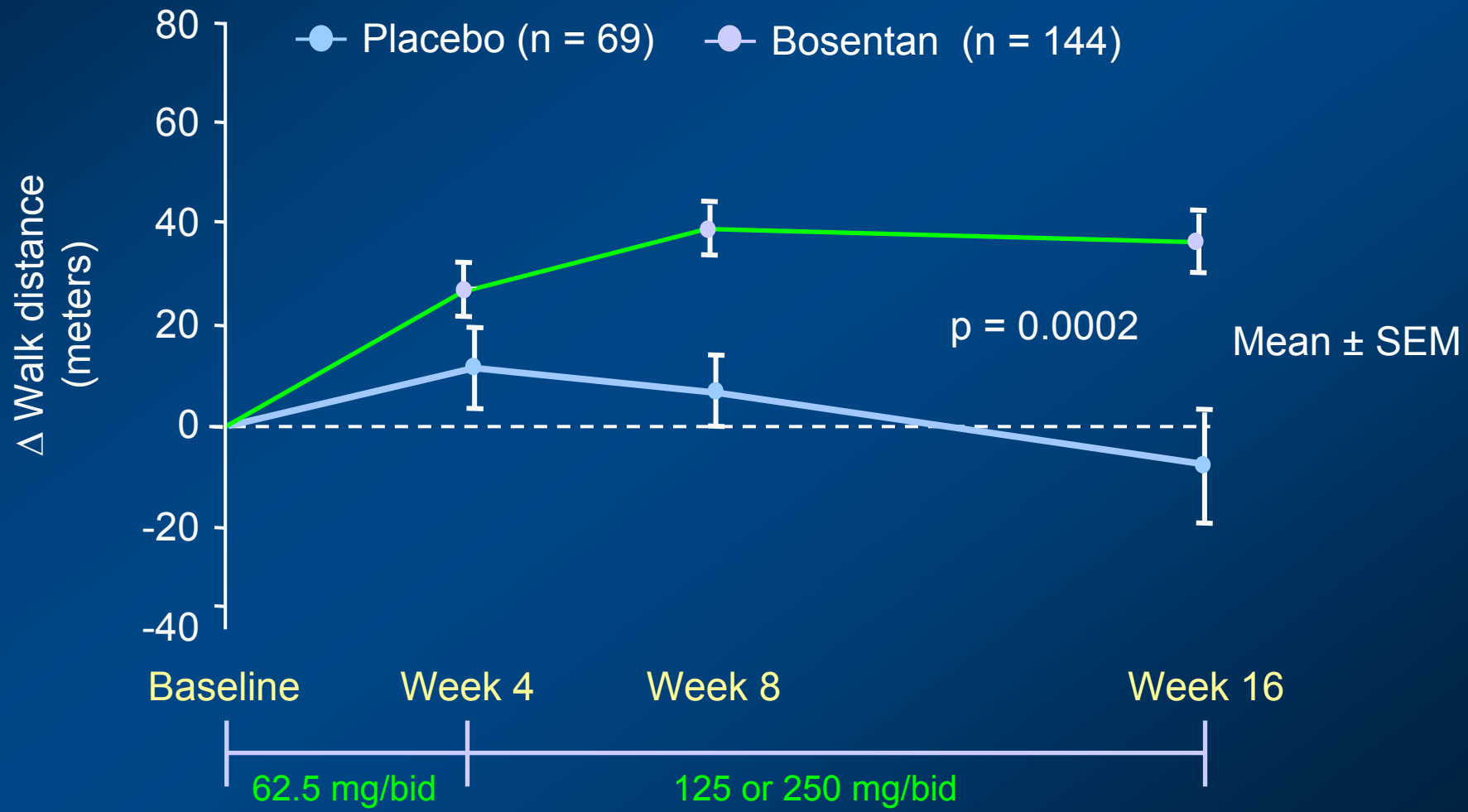
Shortest time to either:

- Death
- Premature withdrawal
- Hospitalization due to PAH worsening
- Initiation of prostacyclin therapy

Rubin et al. NEJM 2002;346:896

Walk test ITT

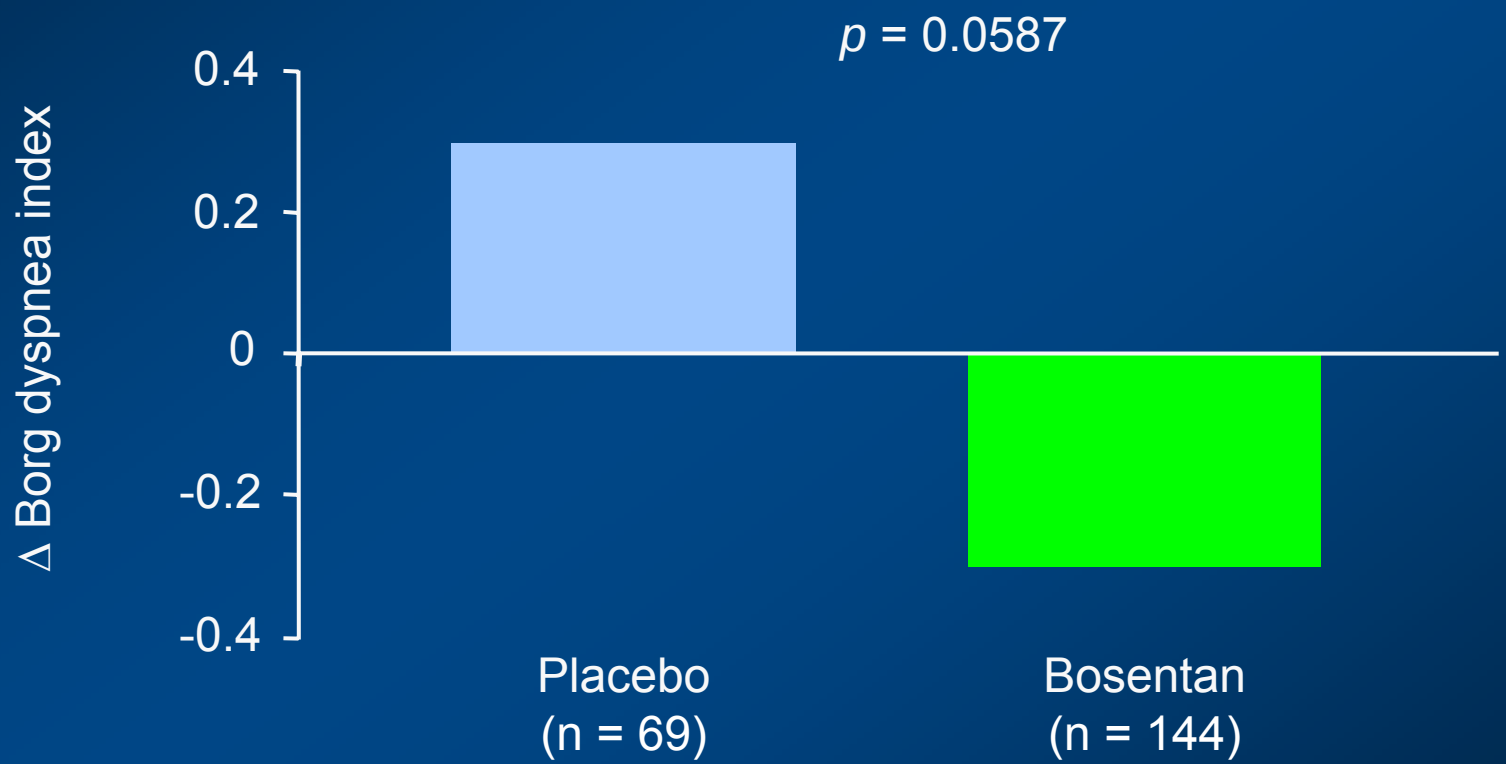
Change from baseline to week 16



Rubin et al. NEJM 2002;346:896

Borg dyspnea index

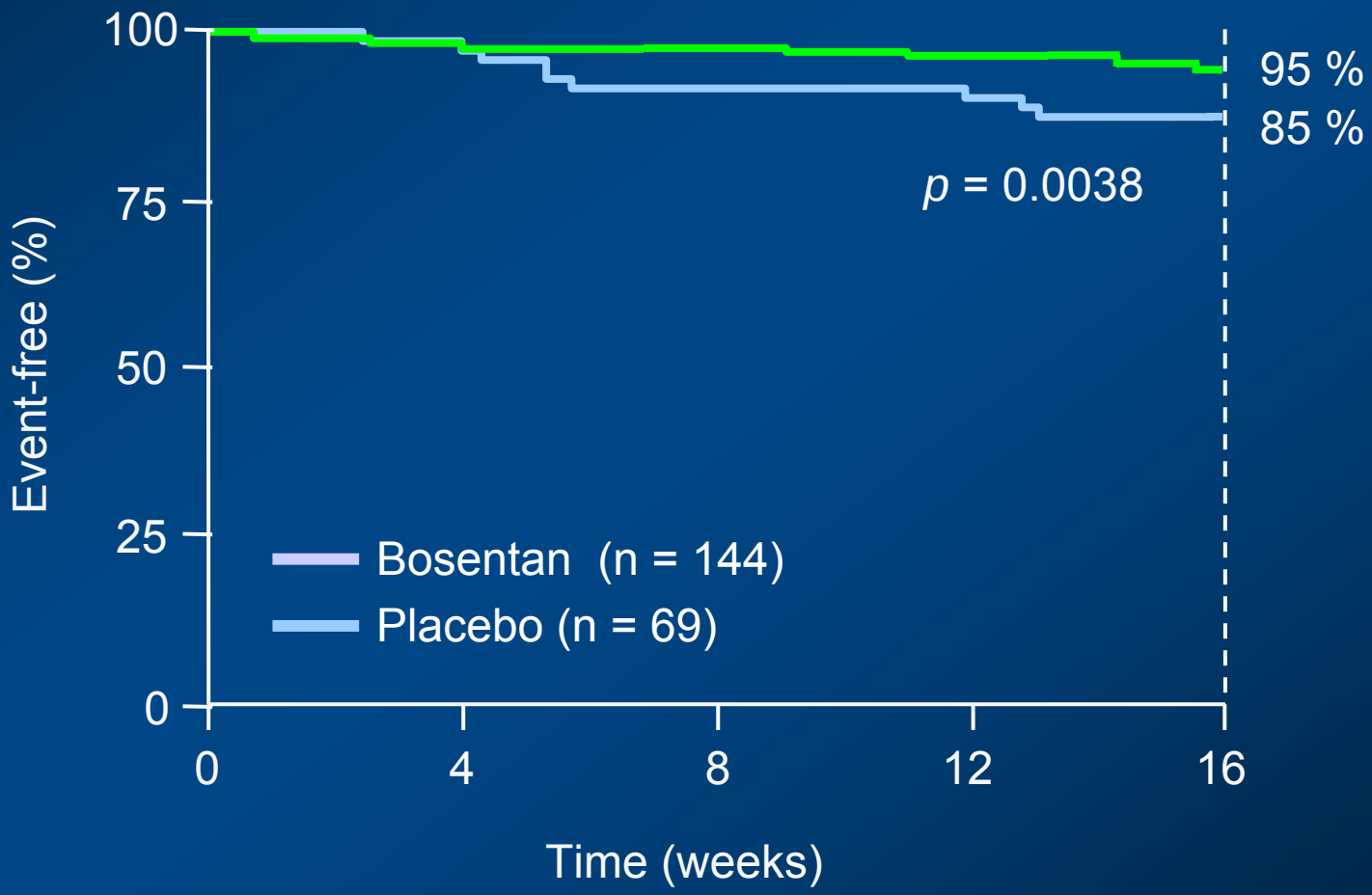
Change from baseline to week 16



Rubin et al. NEJM 2002;346:896

Time to clinical worsening

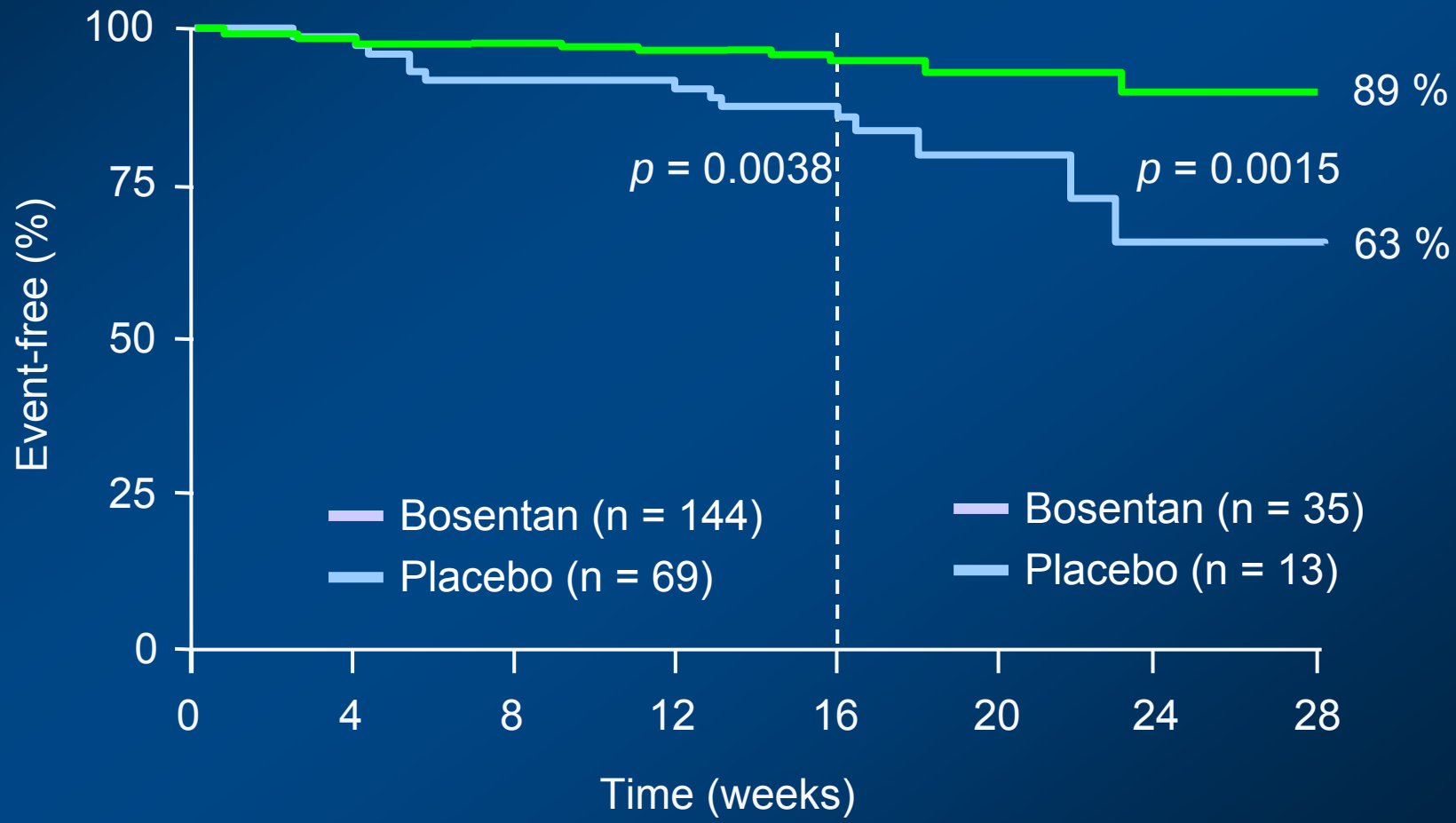
Up to 16 weeks



Rubin et al. NEJM 2002;346:896

Time to clinical worsening

Up to 28 weeks



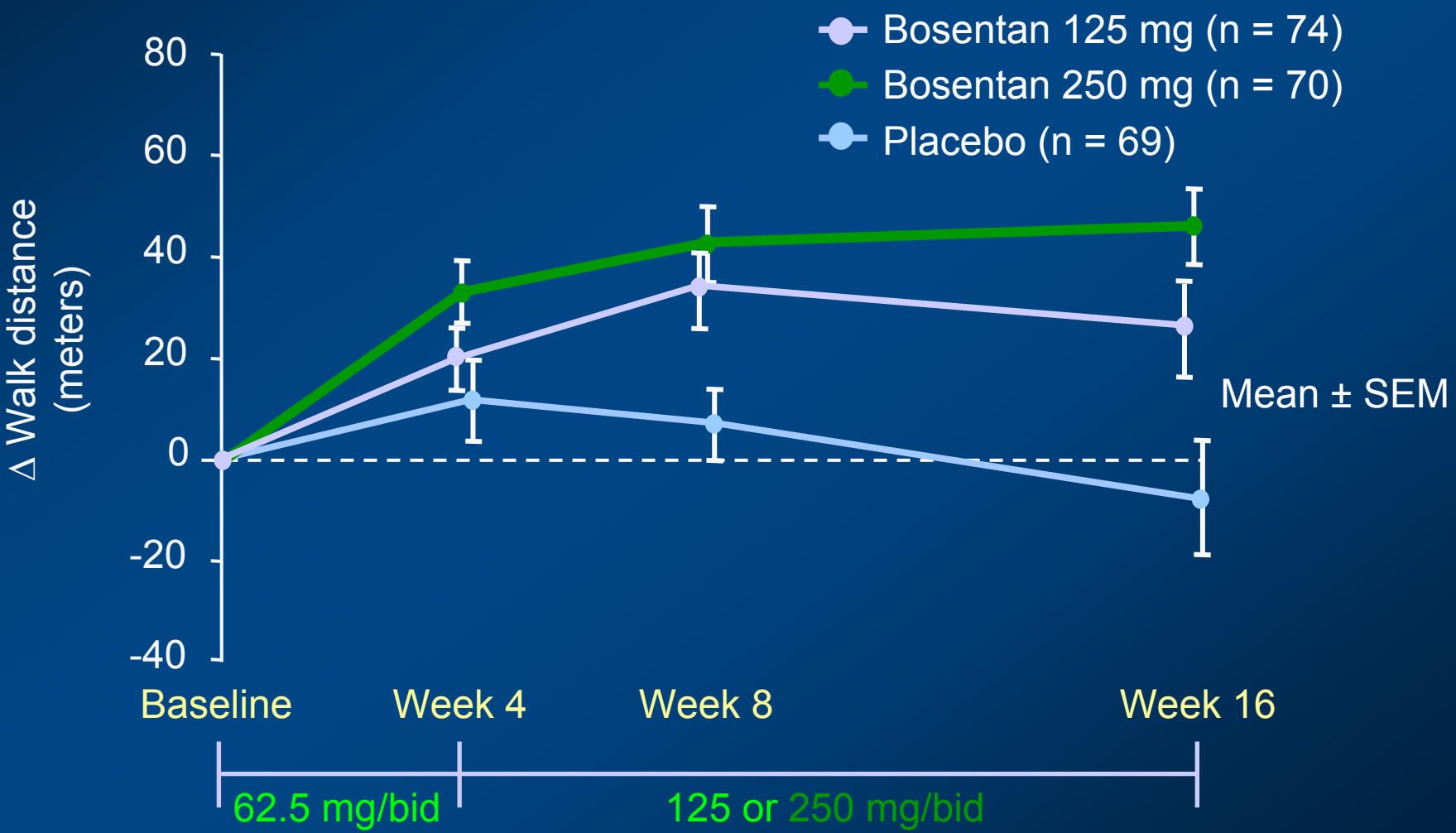
Rubin et al. NEJM 2002;346:896

Dose response

Exploratory analysis

Walk test ITT

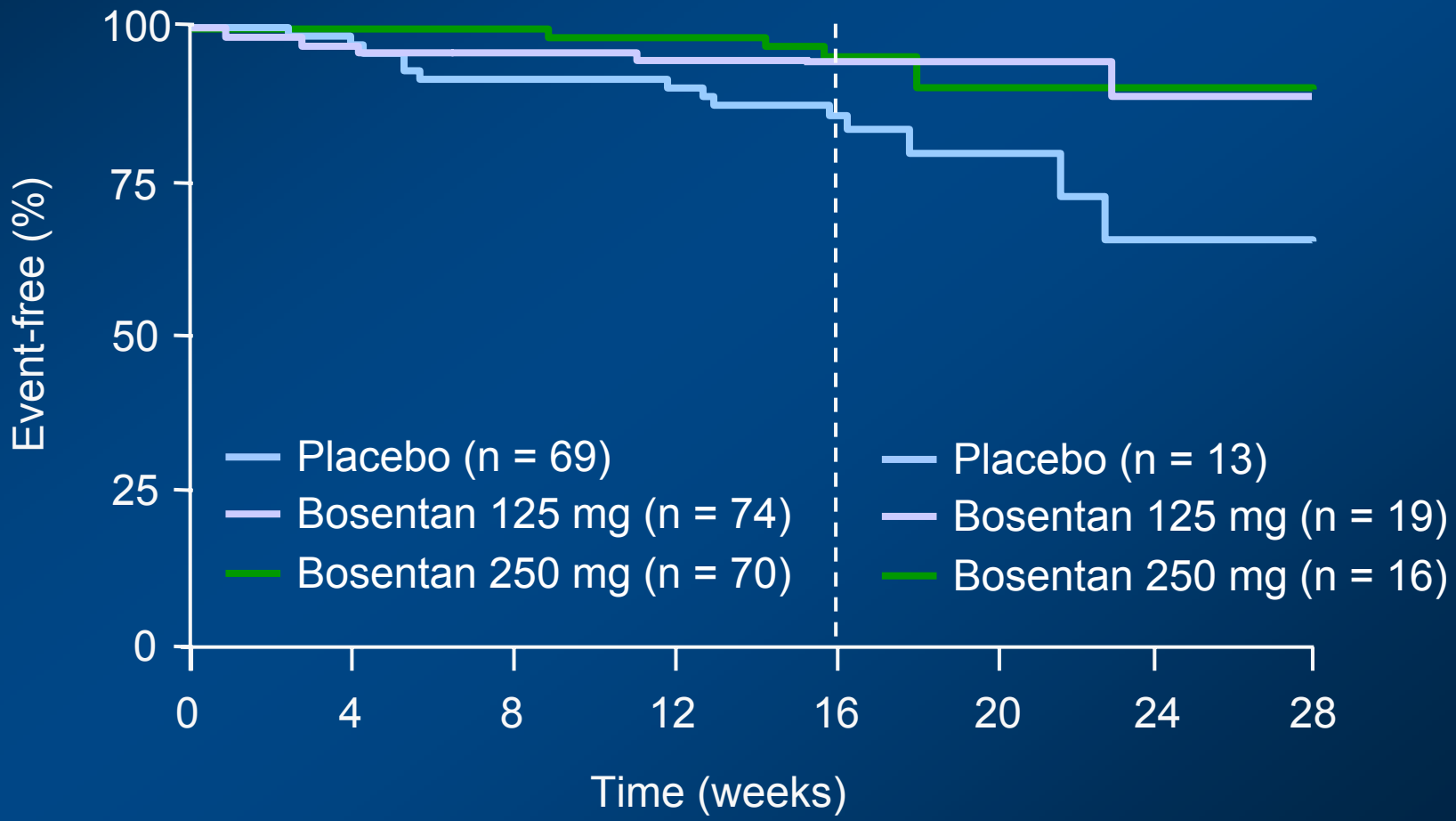
Change from baseline to week 16



Rubin et al. NEJM 2002;346:896

Time to clinical worsening

Up to 28 weeks



Rubin et al. NEJM 2002;346:896

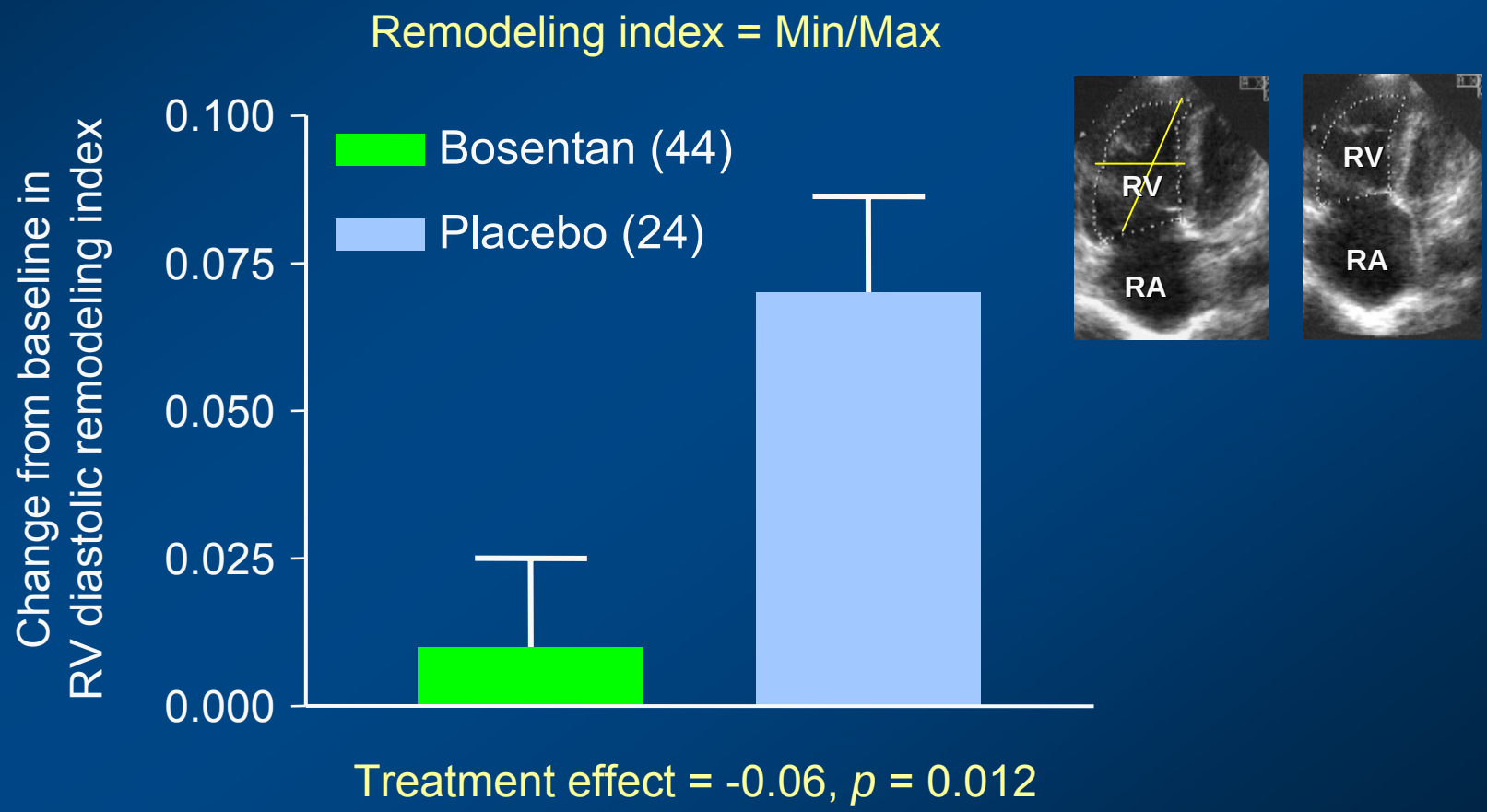
BREATHE-1 maintenance of efficacy

Walk test up to 28 weeks

Frost et al. JACC 2004 (supplement) - abstract

BREATHE-1 echocardiographic substudy: RV diastolic remodeling index

Change from baseline to week 16



Galiè et al. JACC 2003;41:1380

Liver function tests

	Placebo (n = 69)	Bos. 125 mg (n = 74)	Bos. 250 mg (n = 70)
Hepatic function abnormal (investigator-reported)	2 (3%)	3 (4%)	10 (14%)
3X ULN	0 (0%)	10 (14%)	10 (14%)
8X ULN	0 (0%)	2 (2.7%)	5 (7.1%)
Transient cases	- -	7 (10%)	3 (4.3%)
Permanent discontin.	- -	0 (0%)	3 (4.3%)

Actelion: Data on file

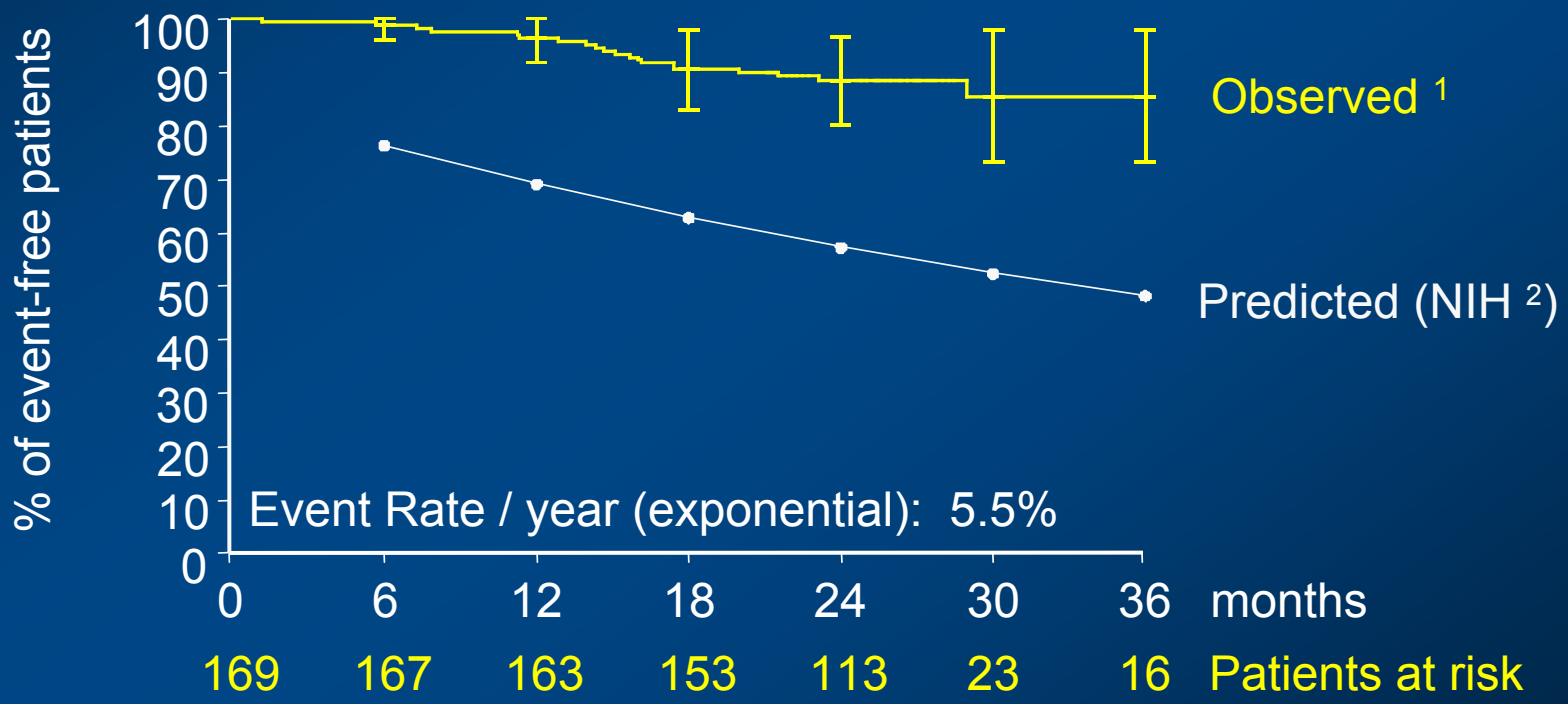
BREATHE-1 Conclusion

Bosentan (Tracleer®) is a dual endothelin receptor antagonist which is an effective oral treatment for patients with PAH

Rubin et al. NEJM 2002;346:896
Galiè et al. JACC 2003;41:1380

Observed and predicted survival

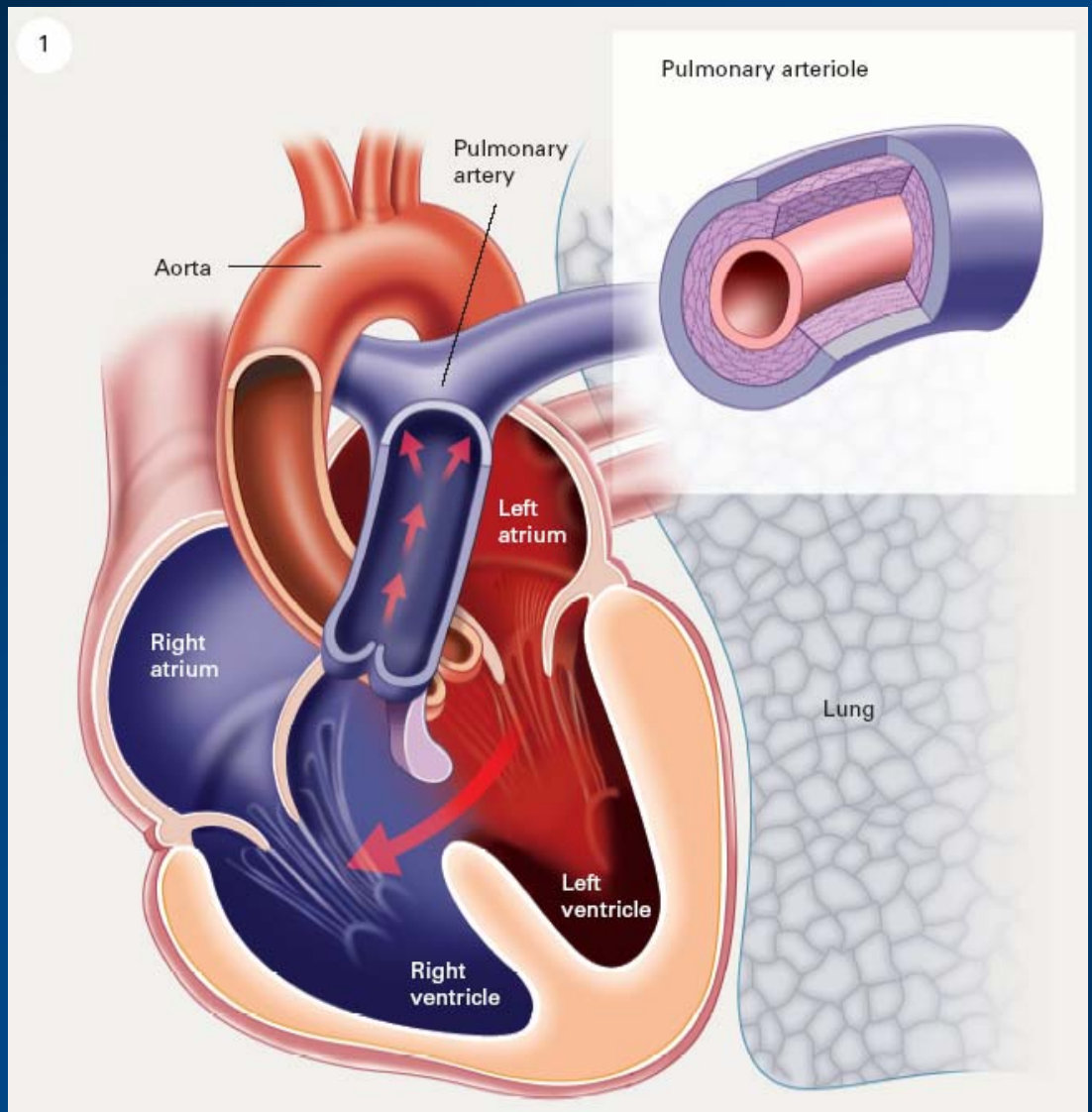
Kaplan-Meier survival estimates with 99% CI



[1] Mc Laughlin et al, Eur Resp J 2005; 25:244-249

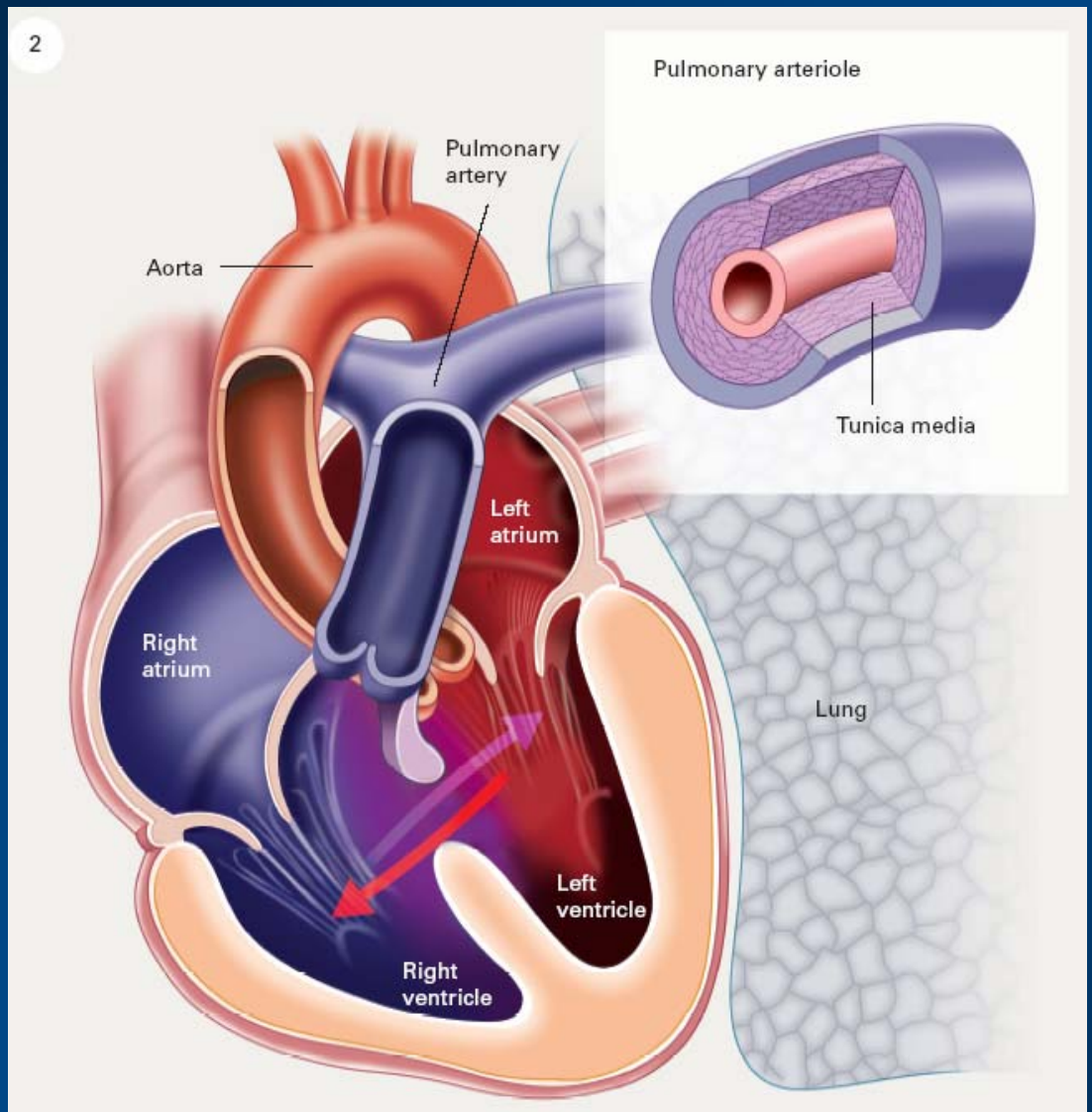
[2] D'Alonzo et al, Ann Intern Med 1991; 115:343

Evolution of Eisenmenger syndrome (1)



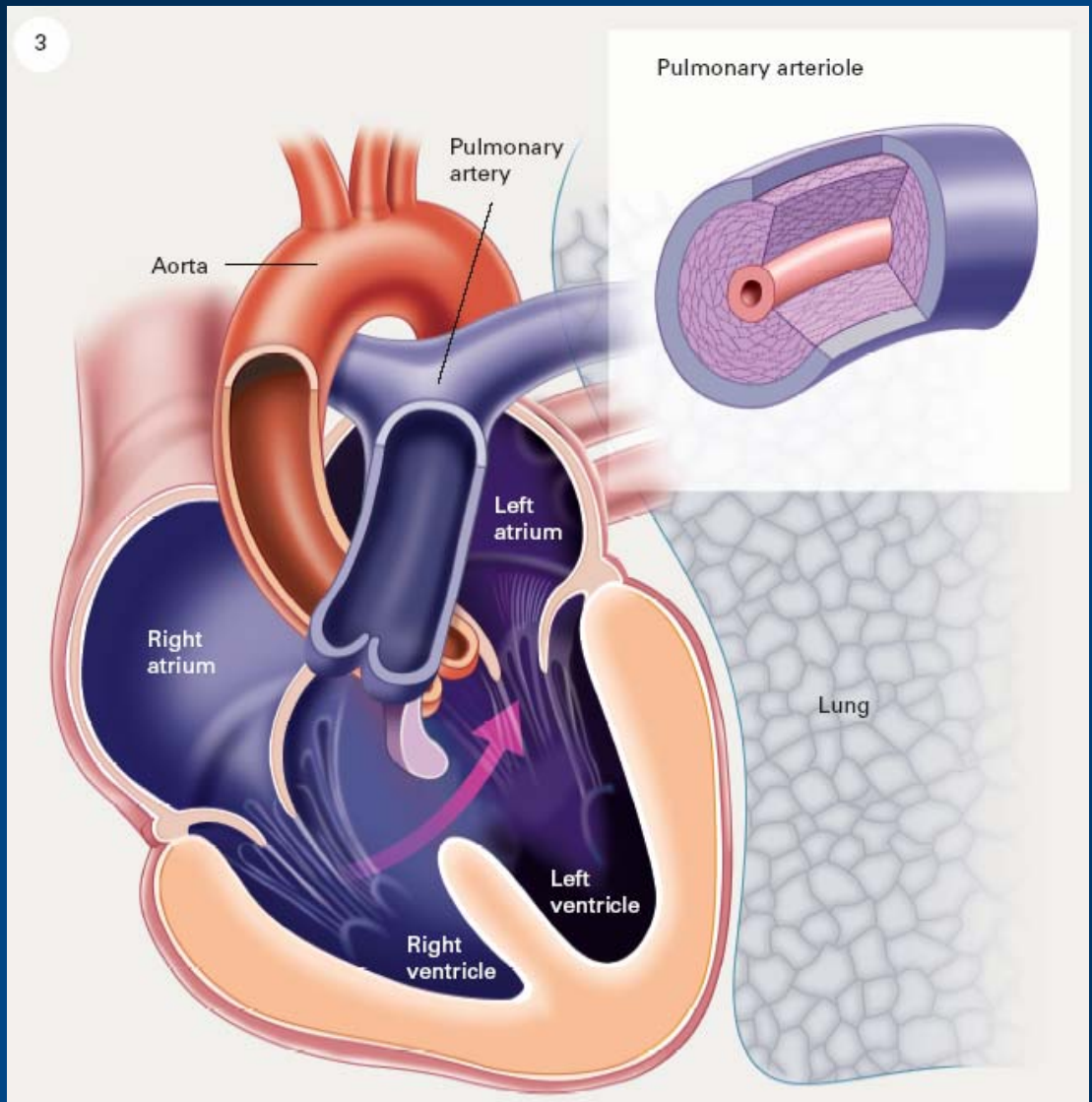
ASD, VSD or complex defect increases pulmonary blood flow via left-to-right shunt

Evolution of Eisenmenger syndrome (2)



Over time, pulmonary resistance rises and results in bi-directional flow

Evolution of Eisenmenger syndrome (3)



Pulmonary artery pressure rises further with reversal of shunt: right-to-left → Eisenmenger syndrome – patient becomes cyanotic

BREATHE-5: Bosentan improves hemodynamics and exercise capacity in the first randomized placebo-controlled trial in Eisenmenger physiology

Nazzareno Galiè, Maurice Beghetti, Michael Gatzoulis,
John Granton, Rolf Berger, Andrea Lauer,
Eleonora Chiossi, Michael Landzberg
on behalf of the BREATHE-5 Investigators

Galiè N, *et al. Circulation* 2006; 114:48-54

Rationale

- ET-1 implicated in Eisenmenger syndrome (1-3)
- Bosentan, a dual ERA, has been shown to be effective in treating PAH
- Small open-label bosentan studies have shown benefits in ES patients (4-7)
- Placebo-controlled study needed to clarify safety and efficacy (8)

(1) Galie N, Cardiovasc Res 2004; 61(2):227-237
(2) Humbert M, J Am Coll Cardiol 2004: S13-S24
(3) Cacoub P, Am J Cardiol 1993; 71(5):448-450
(4) Christensen DD, Am J Cardiol 2004; 94(2):261-263
(5) Gatzoulis MA, Int J Cardiol 2005; 98(1):147-151
(6) Apostolopoulou SC, Heart 2005; 91(11): 1447-1452
(7) Schulze-Neick I, Am Heart J 2005; 150(4):716
(8) Galiè N et al, Circulation 2006; 114:48-54

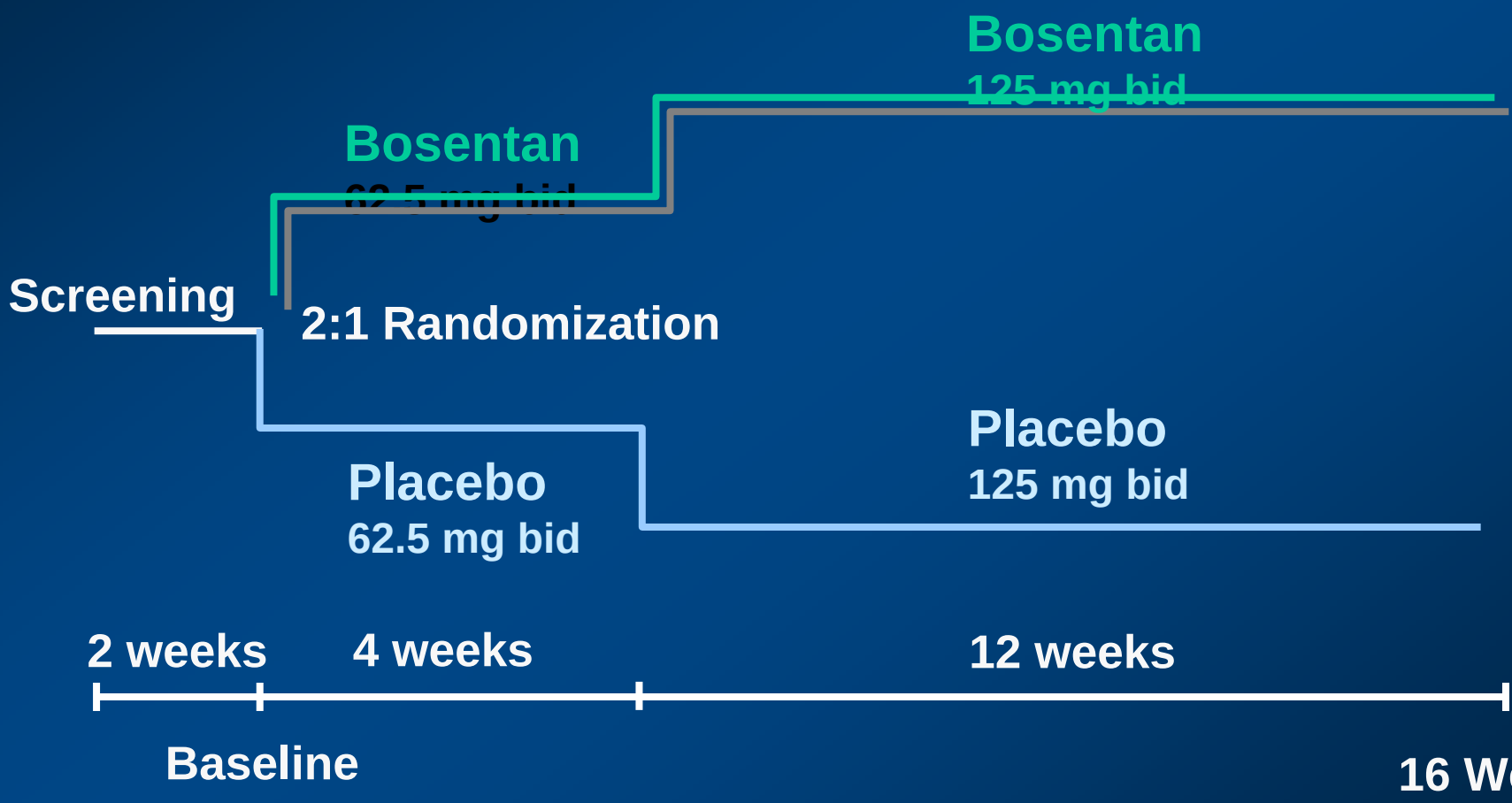
Objectives of the study

To evaluate in a randomized controlled trial in patients with Eisenmenger syndrome the effects of bosentan on:

- **Overall shunting (SpO2)**
- **Cardiopulmonary hemodynamics (PVRi)**
- **Exercise capacity (6MWD)**

Galiè N, *et al. Circulation* 2006; 114:48-54

Study design



Galiè N, *et al. Circulation* 2006; 114:48-54

Bosentan does not reduce $Sp0_2$

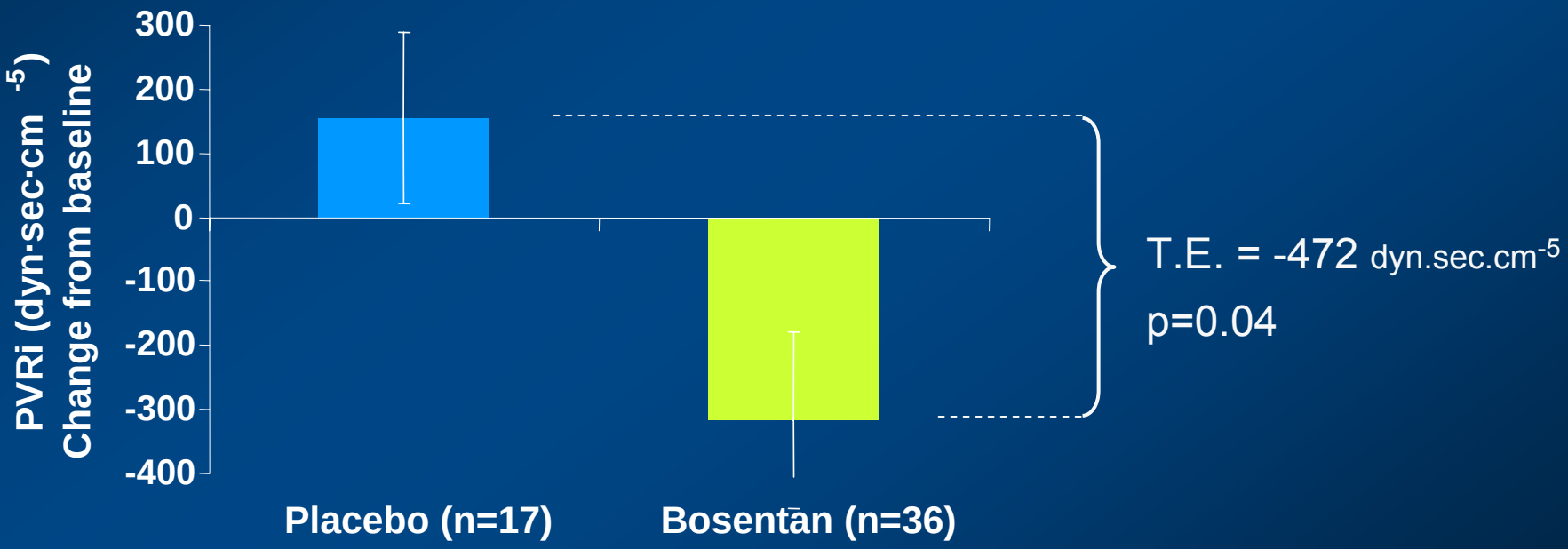
	Placebo (n=17) Mean (SE)	Bosentan (n=35) Mean (SE)
Baseline (%)	83.6 (1.2)	82.4 (0.9)
Week 16 (%)	84.0 (1.6)	83.8 (0.9)
Change from baseline	0.4 (0.9)	1.5 (0.4)

Treatment effect: + 1.0 (0.9)

95 % CI =[-0.7 , 2.8] > -5, non-inferiority shown

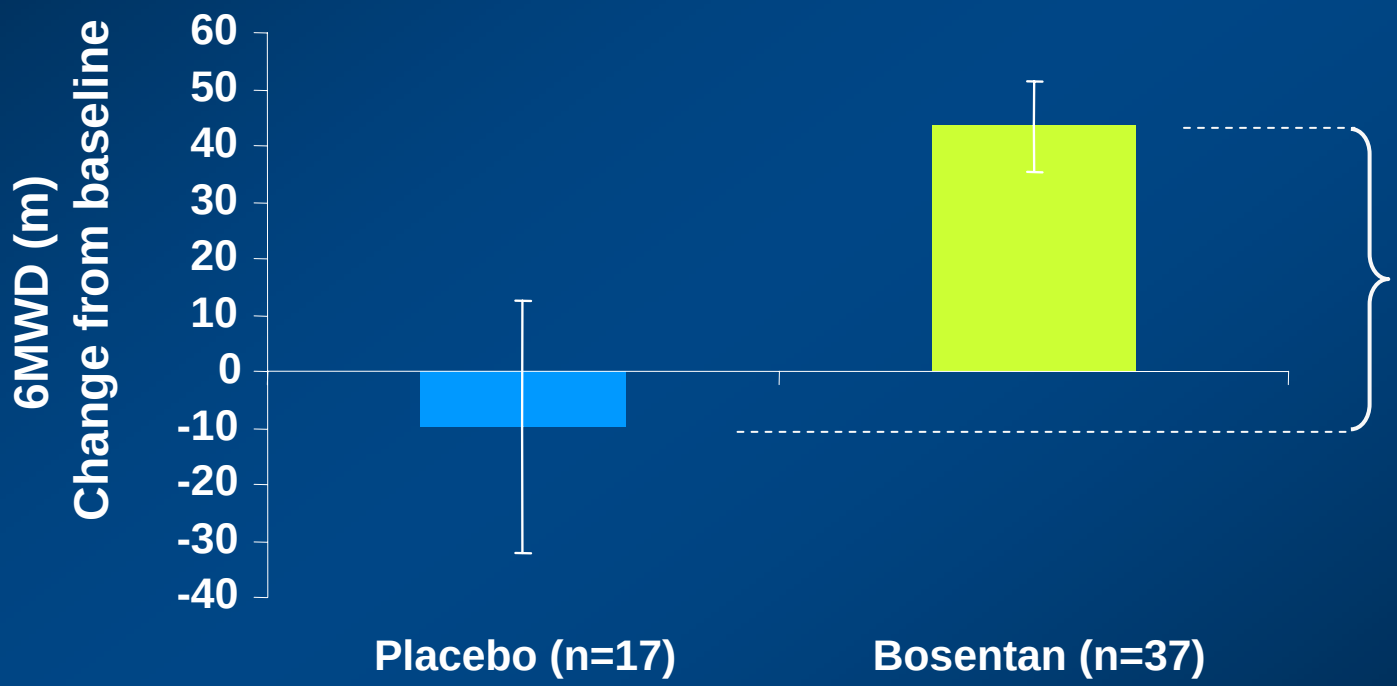
Galiè N, *et al. Circulation* 2006; 114:48-54

Bosentan reduces pulmonary vascular resistance indexed



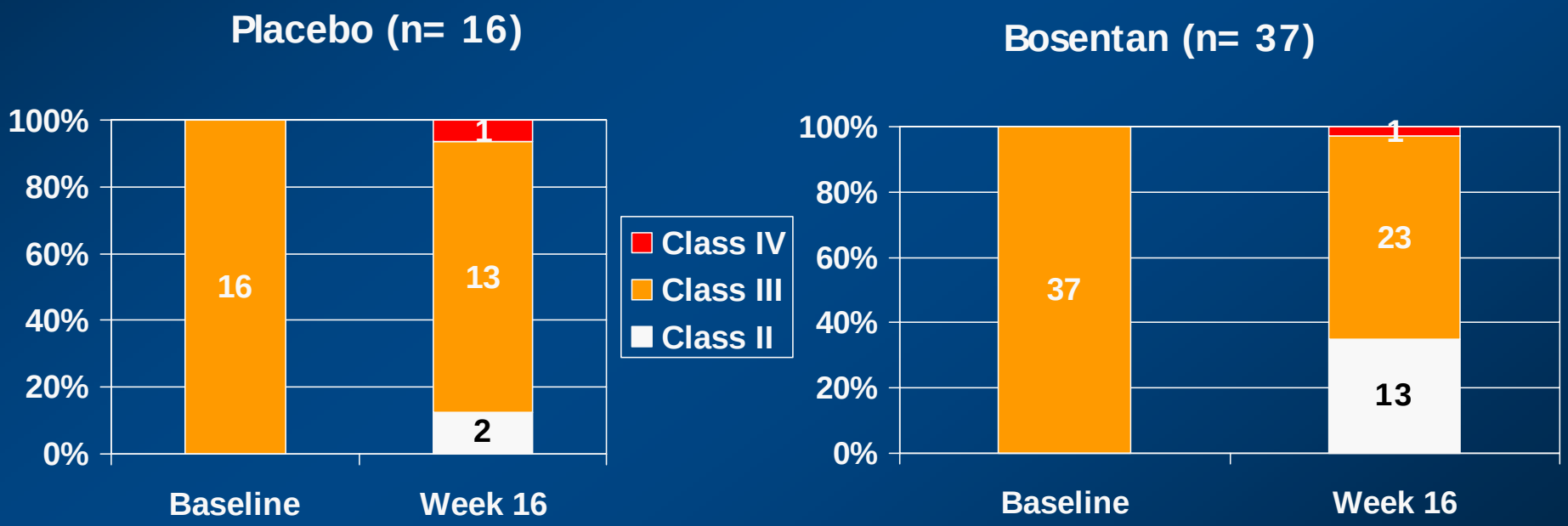
Galiè N, *et al. Circulation* 2006; 114:48-54

Bosentan increases exercise capacity



Galiè N, *et al. Circulation* 2006; 114:48-54

WHO functional class



Galiè N, *et al. Circulation* 2006; 114:48-54