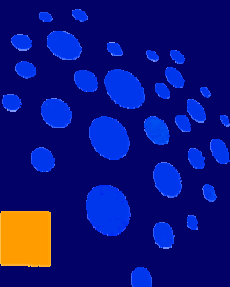


# SIRIUS II

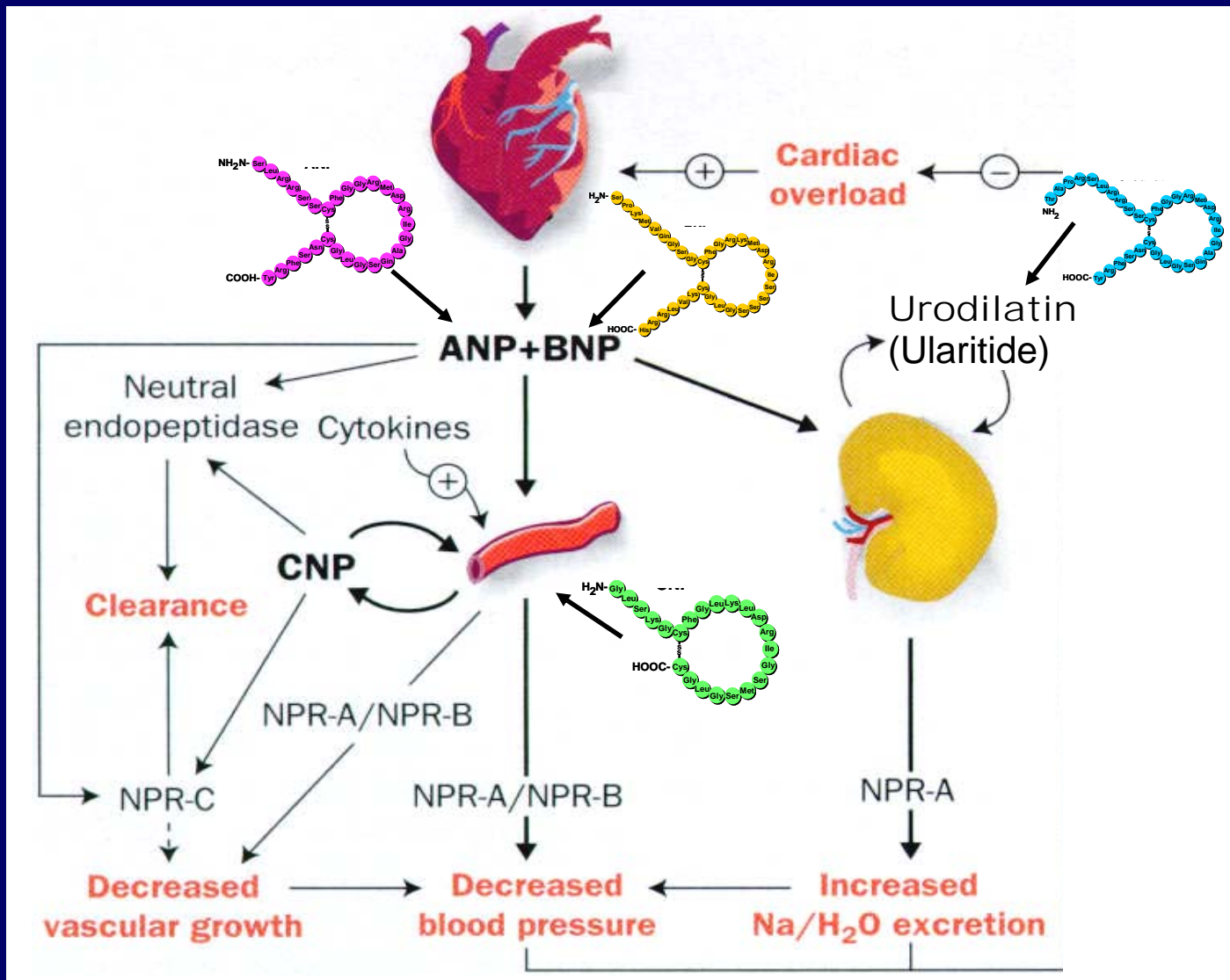
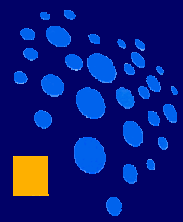
**S**afety and efficacy of an **I**ntravenous placebo controlled  
**R**andomised **I**nfusion of **U**laritide in a prospective  
double-blind **S**tudy in patients with symptomatic,  
decompensated chronic heart failure (Phase IIb)



**Veselin Mitrovic MD, Petar Seferovic MD, Dejan Simeunovic MD,  
Milutin Miric MD, Valentin S. Moiseyev MD, Zhanna Kobalava MD,  
Klaus Nitsche MD, Wolf-Georg Forssmann MD,  
Hartmut Lüss MD and Markus Meyer MD**



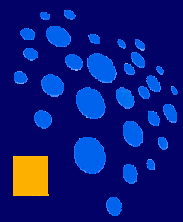
# Physiological Function of Natriuretic Peptides



Adapted from Wilkins MR. Redondo J. Brown LA. *Lancet* 1997;349:1307-1310



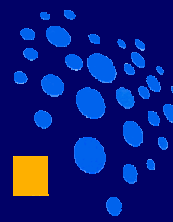
# SIRIUS II - Study Design



- Randomized, double-blind, placebo-controlled, phase II study
- 4 treatment groups: placebo, 7.5, 15 and 30 ng/kg/min over 24 h
- 19 study centres: Germany (13 sites), Russia (4 sites), and Serbia-Montenegro (2 sites)
- 221 patients randomized

Placebo:53 pts. 7.5 ng:60 pts. 15 ng:53 pts. 30 ng:55 pts.

# SIRIUS II – Study Endpoints



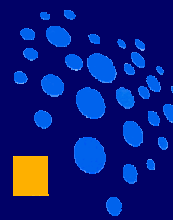
## Primary Endpoints:

- Change in PCWP at 6 hrs compared to placebo
- Change in patient-assessed dyspnea at 6 hrs compared to placebo

## Main Secondary Endpoints:

- Haemodynamic parameters (RAP, PAP, CI, SVR, SV)
- Renal function (through 72 hrs)
- Safety
- 30-day mortality

# SIRIUS II – Study Population



## Main Inclusion Criteria

- Symptomatic, decompensated chronic heart failure
- Dyspnea at rest or during minimal activity
- PCWP  $\geq$  18 mmHg
- CI  $\leq$  2.5 l/min/m<sup>2</sup>

## Main Exclusion Criteria

- Systolic BP  $\leq$  90 mmHg
- Volume depletion or cardiogenic shock
- Mechanical ventilation

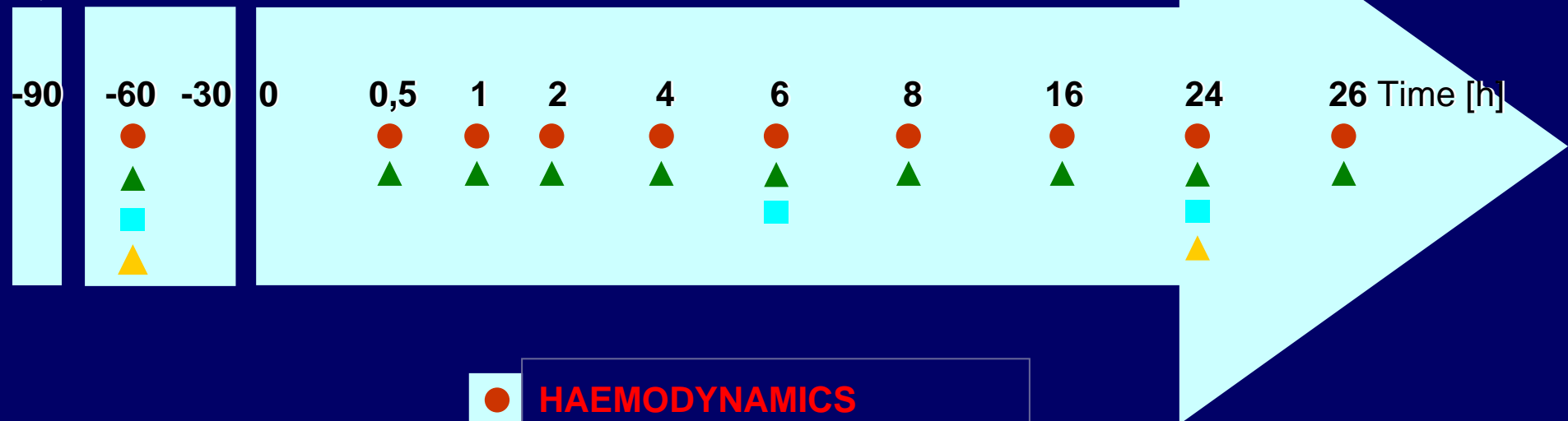
## Restricted Concomitant Medication

- IV vasoactive agents (e.g. nitroprusside, nitroglycerine)
- IV diuretics, ACE-inhibitors, and PDE inhibitors
- New infusion of dobutamine and dopamine

# STUDY FLOW CHART

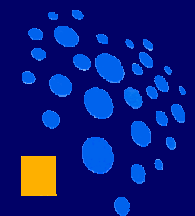
SCREEN CONTROL INFUSION POST INF.

SG-CATH.



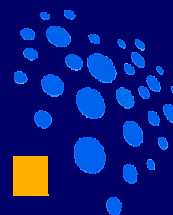
● HAEMODYNAMICS  
▲ PK + HORMONES  
■ DYSPNOEA ASSESSMENT  
▲ CLIN. CHEMISTRY

# Demographics and Baseline Haemodynamics



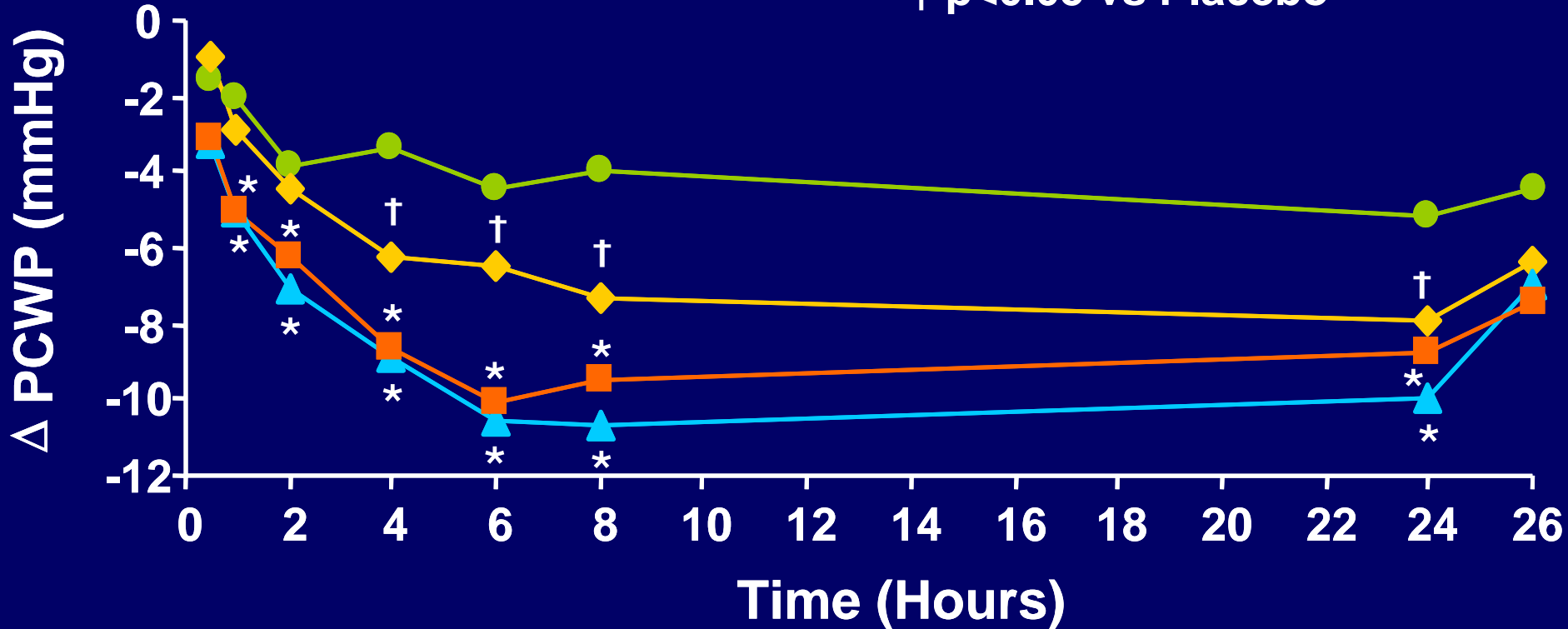
Demographics	All subjects (N=220)
Age (mean, yrs)	61
Male/Female (%)	78 / 22
Cause of Heart Failure	
Ischaemic cardiomyopathy (%)	52
Dilated cardiomyopathy (%)	36
Hypertensive heart disease (%)	11
Baseline Haemodynamics (mean)	
Sys BP (mean, mmHg)	125
PCWP (mean, mmHg)	25
CI (l/min/m <sup>2</sup> )	1.9
EF < 30% (%)	72
EF < 40% (%)	94
NT-pro-BNP (median, pg/ml)	3,200

# Ularitide Reduces PCWP



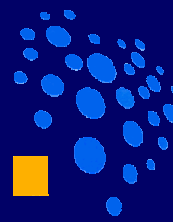
\* p<0.01 vs Placebo

† p<0.05 vs Placebo

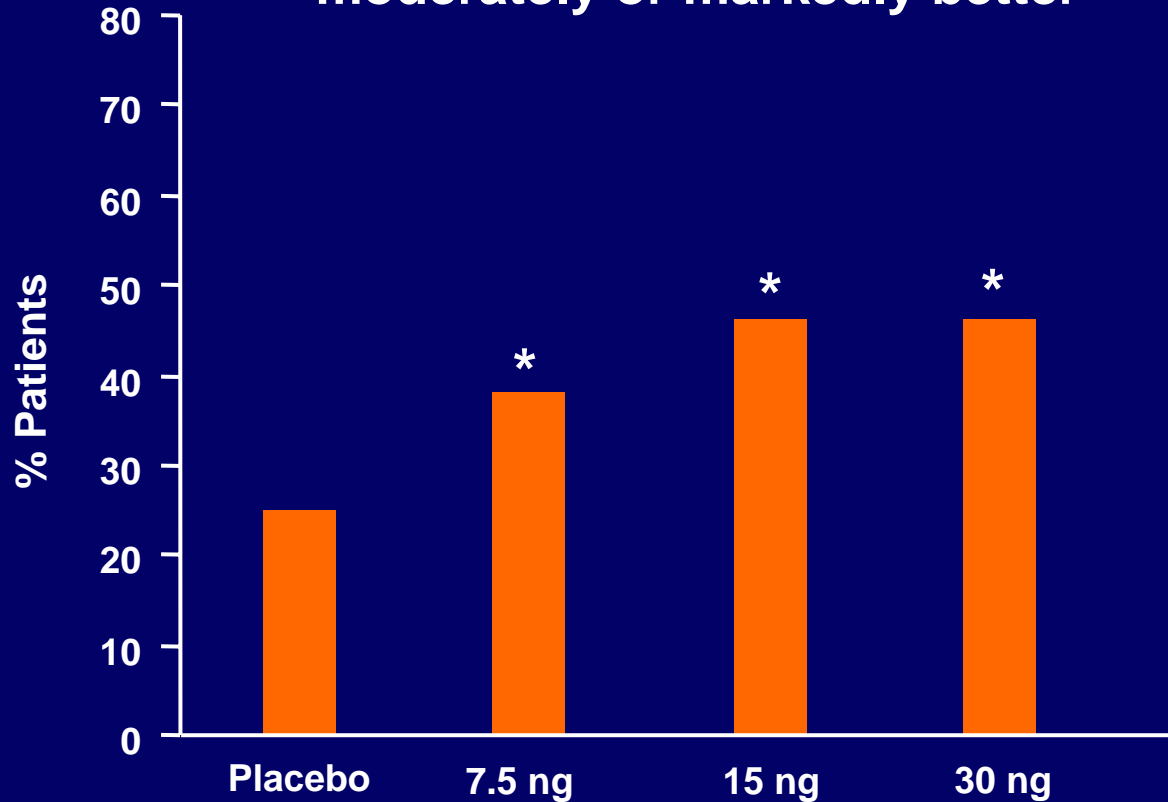


● Placebo    ◆ 7.5 ng/kg/min    ▲ 15 ng/kg/min    ■ 30 ng/kg/min

# Ularitide Improves Dyspnea Categories

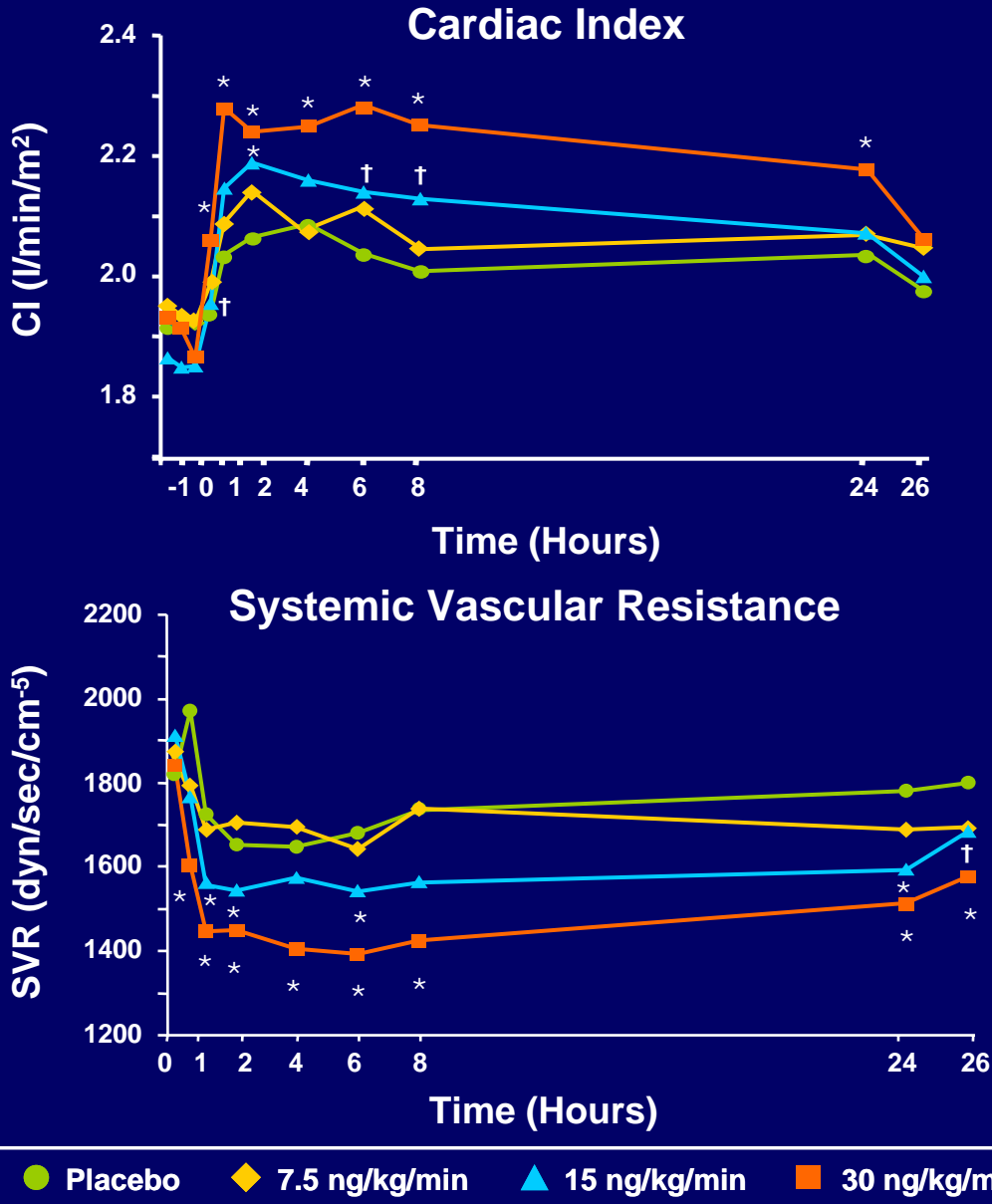


Patient-assessed dyspnea at 6 hrs:  
moderately or markedly better

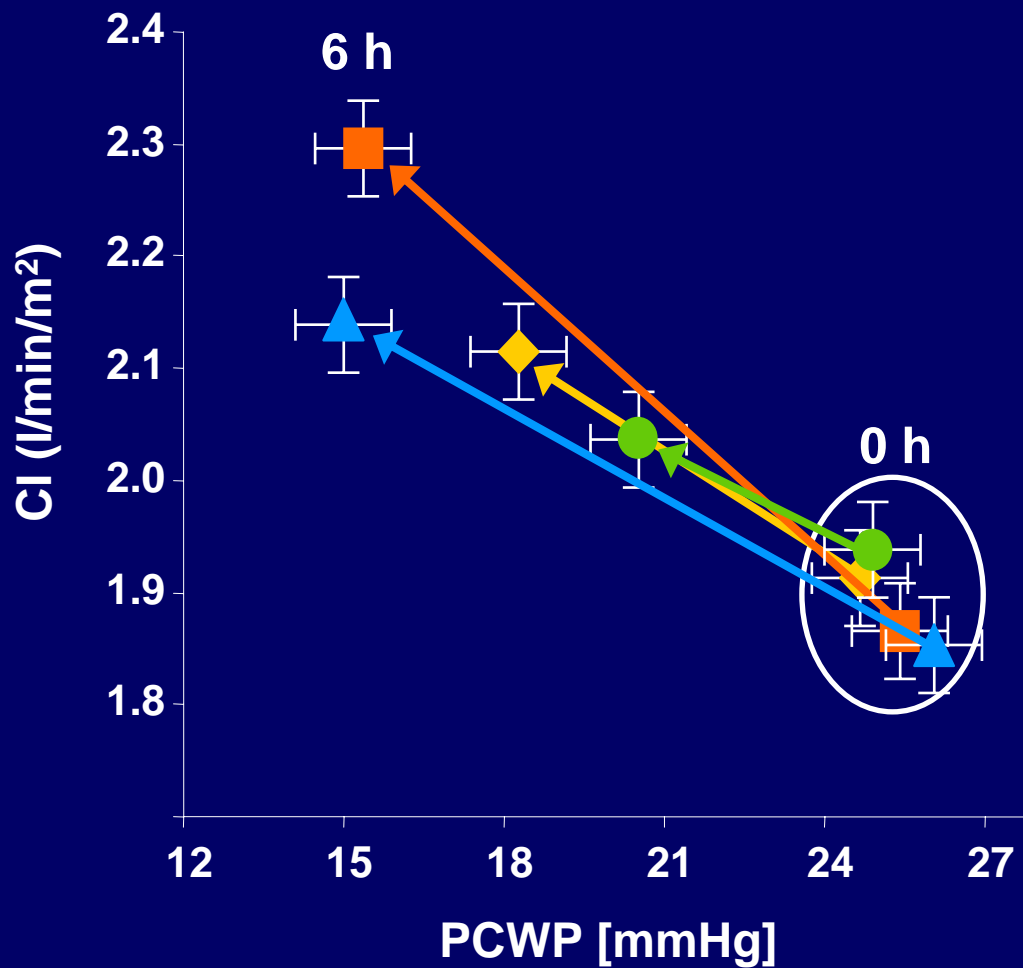
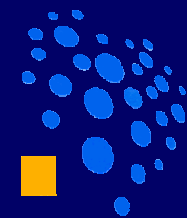


\*  $p < 0.05$  vs Placebo

# Ularitide Improves Cardiac Function

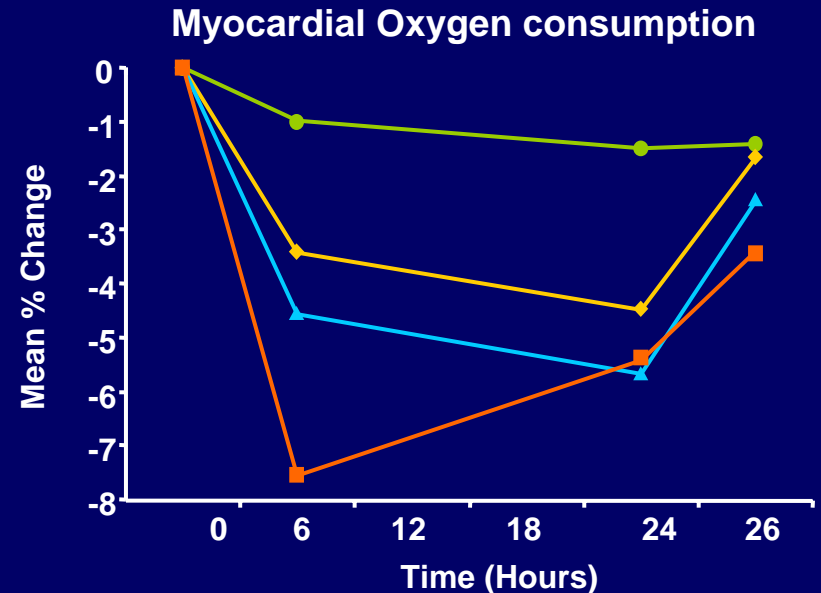
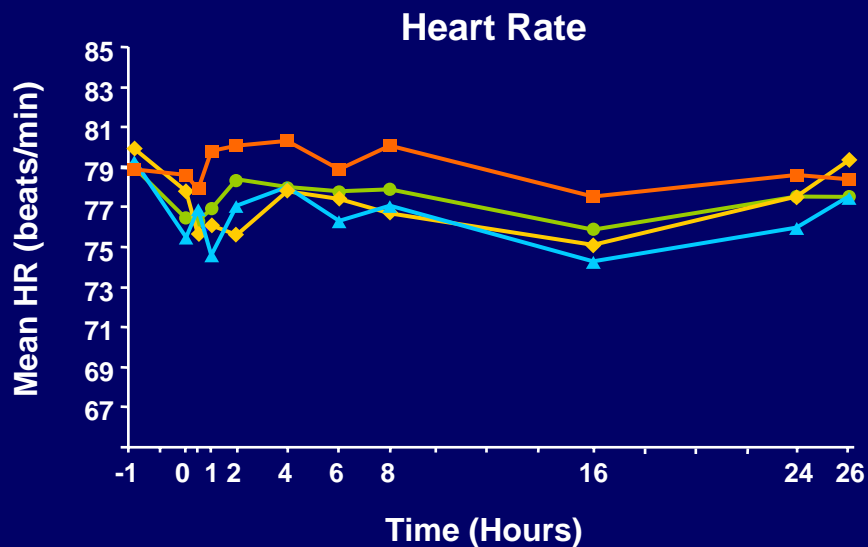
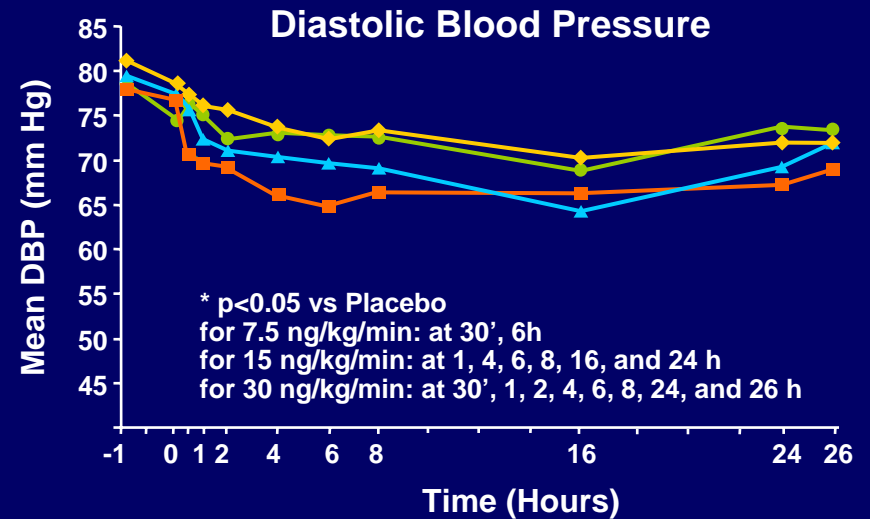
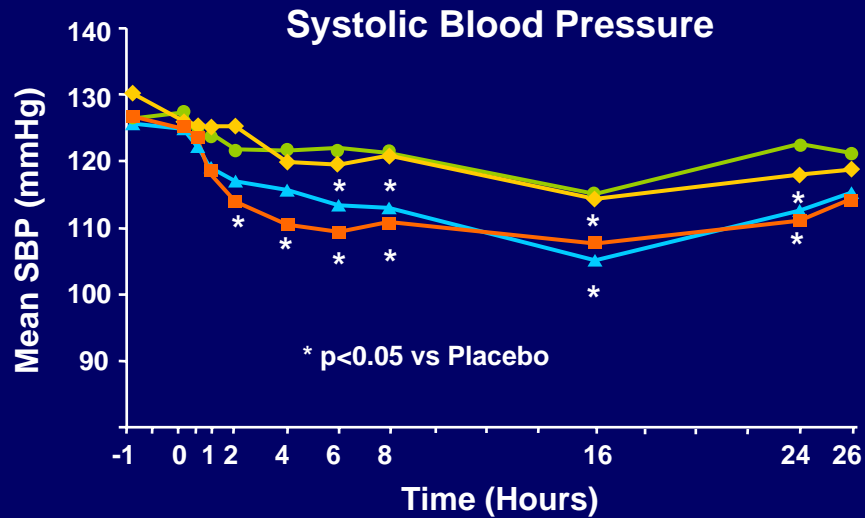


# Effect of Ularitide on Left-Ventricular Pump Function

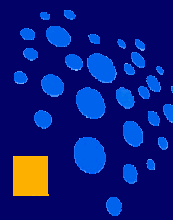


● Placebo    ◆ 7.5 ng/kg/min    ▲ 15 ng/kg/min    ■ 30 ng/kg/min

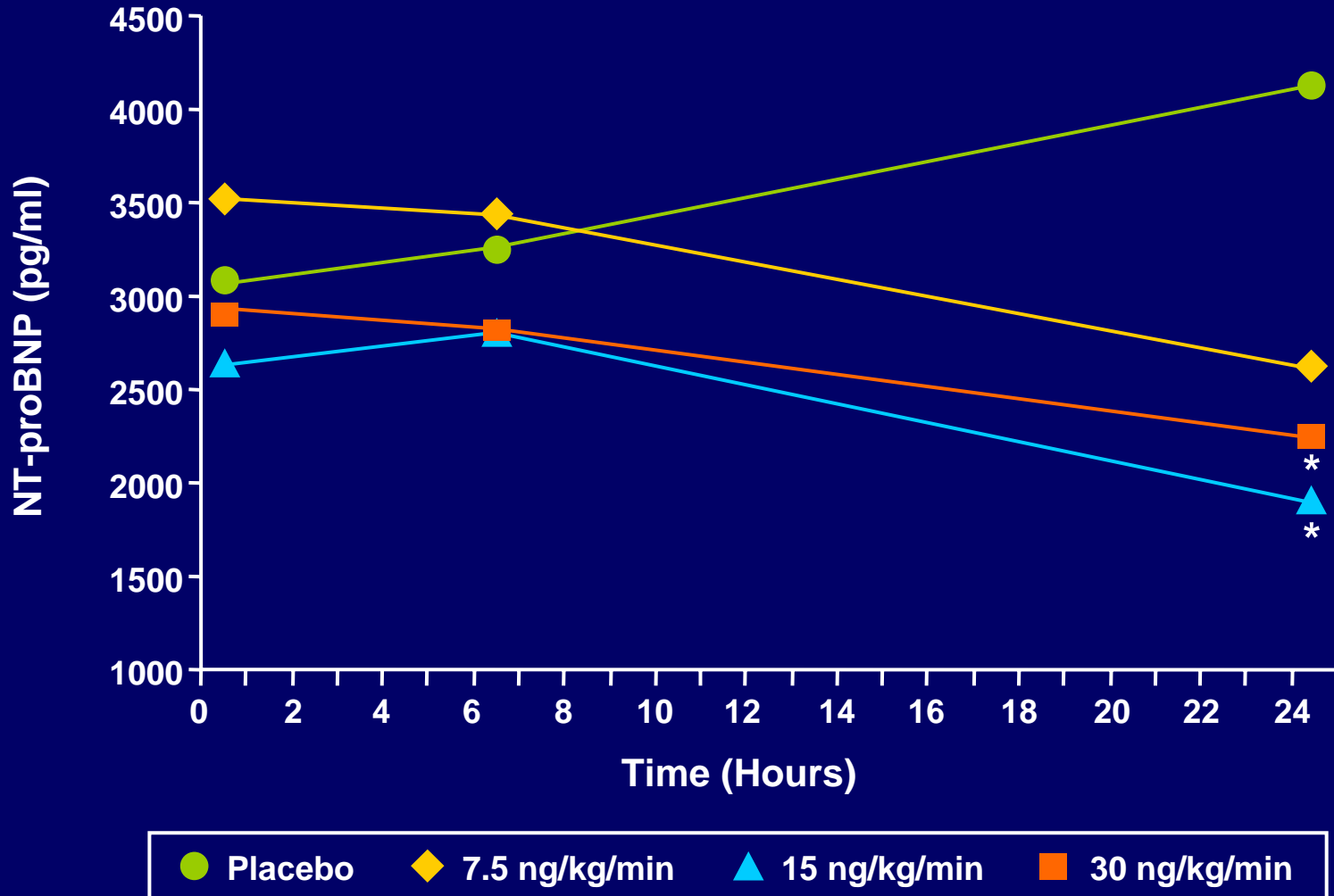
# Effects of Ularitide on Blood Pressure, Heart Rate and Myocardial O<sub>2</sub> - Consumption



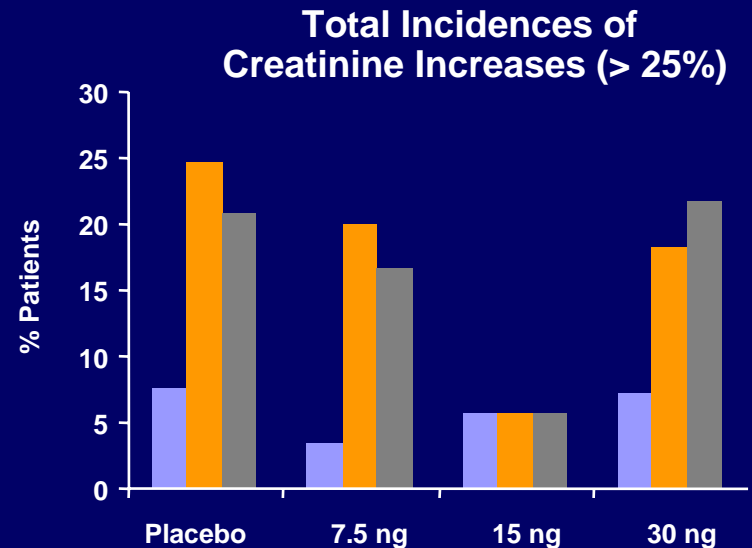
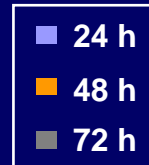
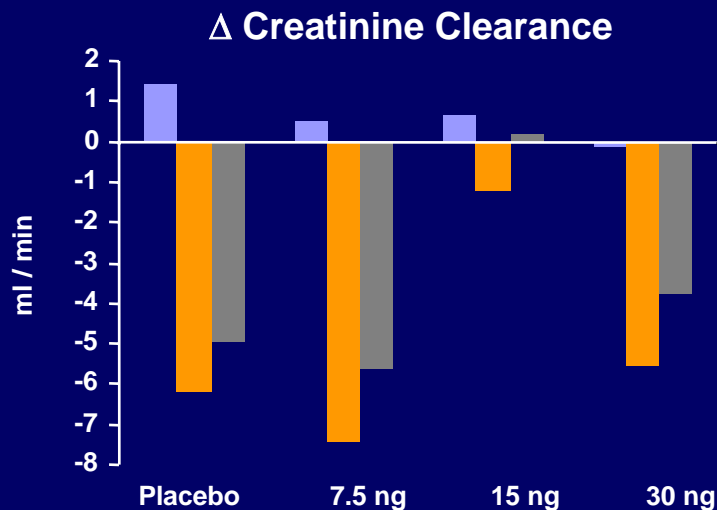
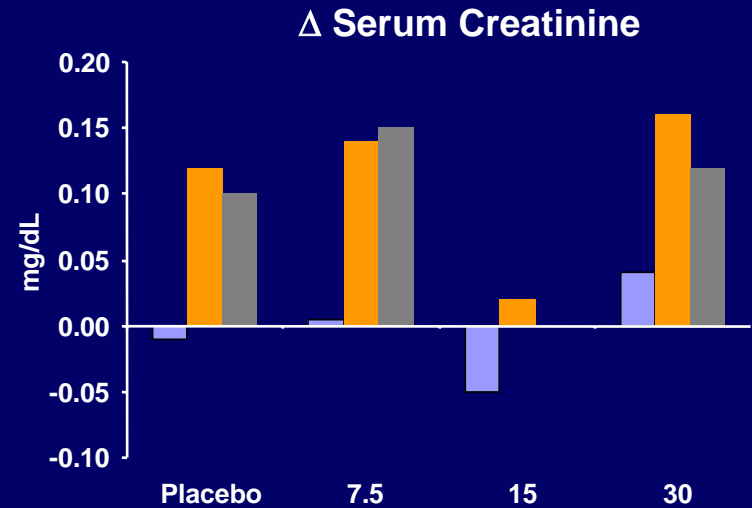
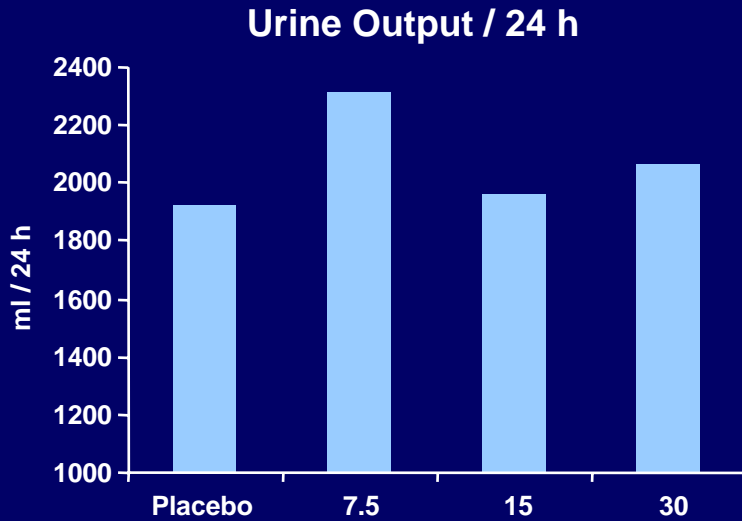
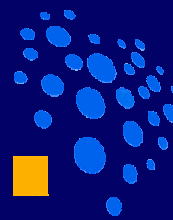
# Ularitide Reduces NT – pro BNP Levels



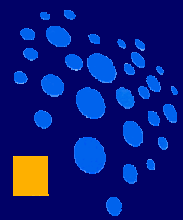
\*  $p < 0.05$  vs Placebo



# Ularitide Does Not Worsen Renal Function Through 72 Hours

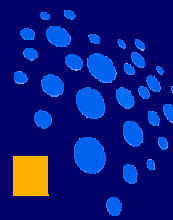


# SIRIUS II – Safety Summary



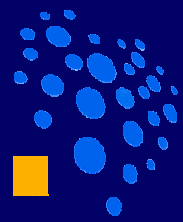
- Frequency of AEs was greater in the ularitide groups compared to placebo
- Most frequently reported AEs: hypotension (6.5%), blood pressure decrease (5.4%), cardiac failure (4.8%), dizziness (3.6%)
- Frequency of SAEs was increased in placebo patients compared with ularitide groups
- 12 patients died during the 30-day follow-up period
  - Placebo: 7 pts. 7.5 ng: 2 pts. 15 ng: 2 pts. 30 ng: 1 pt.

# SIRIUS II – Safety



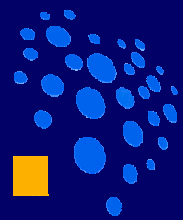
	<b>Placebo (n=53)</b>	<b>7.5 ng/kg/min (n=60)</b>	<b>15 ng/kg/min (n=53)</b>	<b>30 ng/kg/min (n=55)</b>
<b>Hypotensions During Infusion n (%)</b>	<b>1 (1.9)</b>	<b>5 (8.3)</b>	<b>6 (11.3)</b>	<b>9 (16.4)</b>
<b>Serious Adverse Events (day 1-30) n (%)</b>	<b>9 (17)</b>	<b>5 (8.3)</b>	<b>5 (9.4)</b>	<b>6 (10.9)</b>
<b>30-day Mortality n (%)</b>	<b>7 (13.2)</b>	<b>2 (3.3)</b>	<b>2 (3.8)</b>	<b>1 (1.8)</b>

# Summary



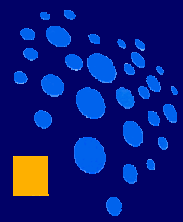
- Ularitide significantly reduced PCWP with early and sustained effects during infusion.
- Ularitide significantly improved patient-assessed dyspnea at 6 hours.
- Clinical and haemodynamic effects were reflected by decreased NT-proBNP.
- Most frequently reported AEs were dose-dependent decreased BP.

# Summary



- Ularitide did not worsen renal function through 72 hours.
- Length of hospital stay was reduced in the two highest dose groups.
- 30-day mortality was lower in all active treatment arms compared to placebo.

# Conclusions



- Ularitide is haemodynamically active and has beneficial clinical effects in patients with symptomatic decompensated heart failure
- Ularitide is well-tolerated at doses up to 30 ng/kg/min for 24 hours
- Future studies are planned

**Thank you !**