

PN 400 Significantly Improves Upper Gastrointestinal Tolerability Compared with Enteric-Coated Naproxen Alone in Patients Requiring Chronic NSAID Therapy: Results from Two Prospective, Randomized, Controlled Trials

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Introduction

- NSAIDs are commonly used to treat pain and the signs and symptoms of arthritis^{1,2}
- Patient adherence to prescribed chronic NSAID therapy can be impacted by poor UGI tolerability³
- PN 400 is a fixed-dose combination tablet designed to provide sequential delivery of
 - IR esomeprazole (20 mg)
 - EC naproxen (500 mg)
- These two Phase III studies compared the UGI endoscopic efficacy and safety of PN 400 with EC naproxen alone in patients *at risk* of NSAID-associated ulcers

¹Singh et al. Am J Ther. 2000; 7: 115-121

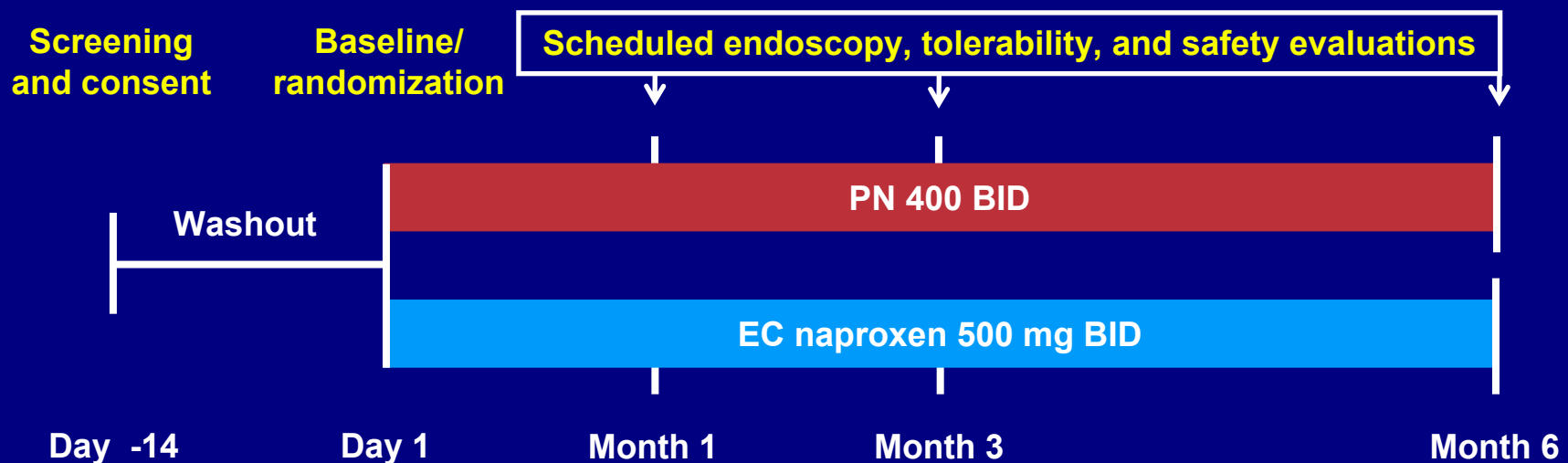
²Laine et al. Gastroenterol. 2001; 120: 594-606

³Lanas et al. Am J Gastroenterol. 2005; 100: 1685-1693

Study design

Two randomized, double-blind, parallel-group, controlled, multicenter studies included *H. pylori*-negative patients

- With OA, RA, or any other condition requiring chronic NSAIDs
- Without GU or DU (≥ 3 mm diameter with depth) at baseline
- Aged ≥ 50 years or 18-49 years with a history of GU or DU within the past 5 years



OA, osteoarthritis; RA, rheumatoid arthritis; GU, gastric ulcer; DU, duodenal ulcer

Study endpoints

- **Primary endpoint:** Cumulative incidence of GUs* throughout 6 months of therapy stratified by LDA use (≤ 325 mg/day)¹
- **Secondary endpoints:**
 - Cumulative incidence of DUs
 - Discontinuations as a result of any AE (including DU)
 - Incidence of pre-specified, NSAID-associated UGI AEs and/or DUs
 - **Change from baseline in SODA scores**
 - **Response on the OTE-DP rating**
 - **Proportion of patients heartburn-free at 6 months**
 - **Discontinuations as a result of pre-specified, NSAID-associated UGI AEs or DUs**

**Patient-
reported
outcomes**

*Mucosal break ≥ 3 mm diameter with depth
SODA, Severity Of Dyspepsia Assessment;
OTE-DP, Overall Treatment Evaluation of Dyspepsia

¹Presented at ACR, Oct 19, 2009

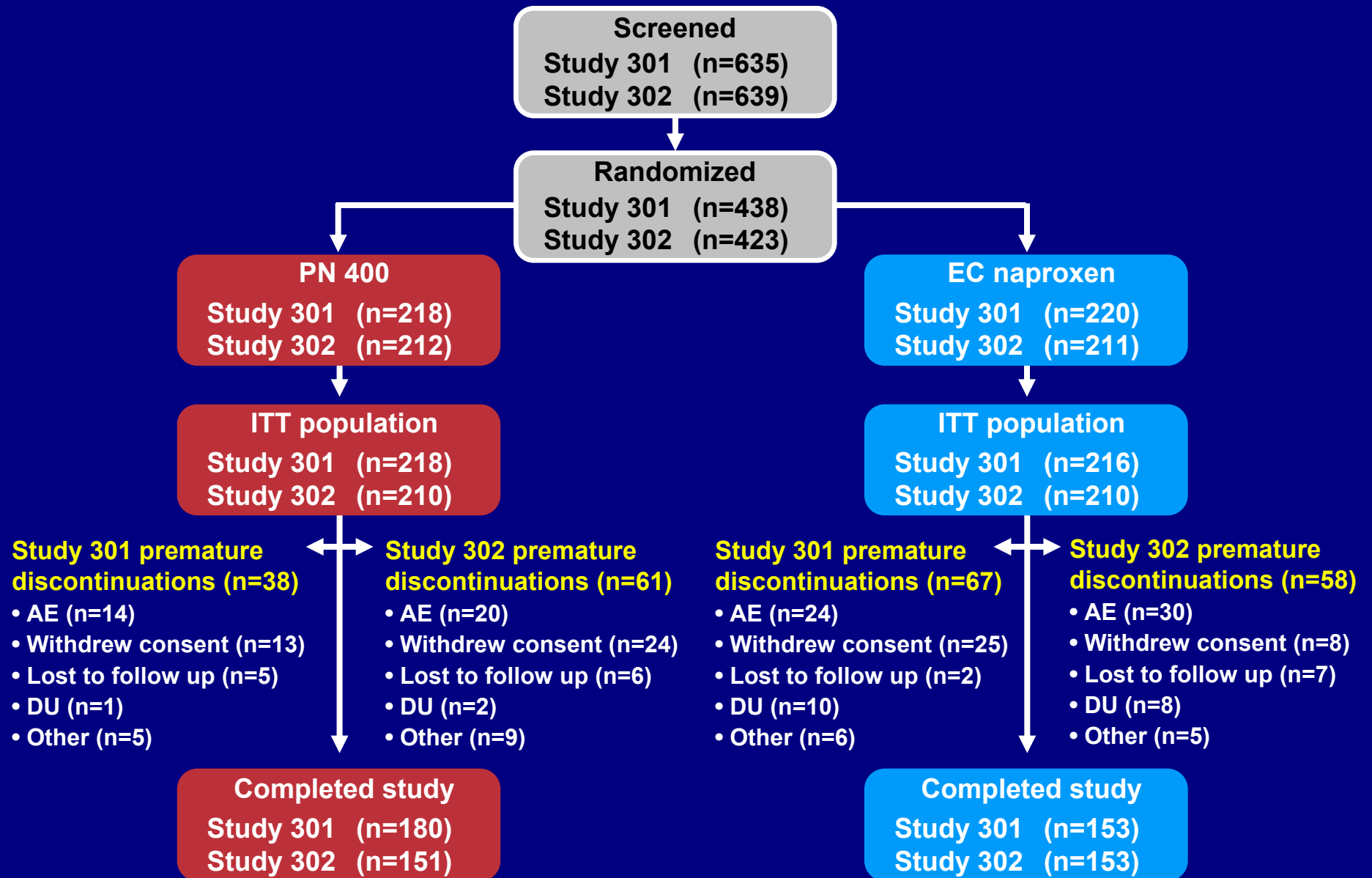
OTE-DP and SODA questionnaires

- **Severity Of Dyspepsia Assessment (SODA)¹**
 - Completed at baseline, 1, 3, and 6 months
 - Comprises 17 questions and 3 domains
 - ◆ **Dyspepsia Pain Intensity** – during previous 7 days
 - ◆ **Non-pain Symptoms** – during previous 7 days
 - ◆ **Satisfaction with dyspepsia-related health**

- **Overall Treatment Evaluation of Dyspepsia (OTE-DP)**
 - Derivative of the Global Ratings of Change Questionnaire²
 - Assessed at Month 6 or withdrawal
 - Responses were rated as “Better”, “Worse”, or “Same”
 - Patients reporting changes were asked about the degree of change

¹Rabeneck et al. Rheumatol. 2003; 42 (3): iii32-39

²Jaeschke et al. Control Clin Trials 1989; 10: 407-415

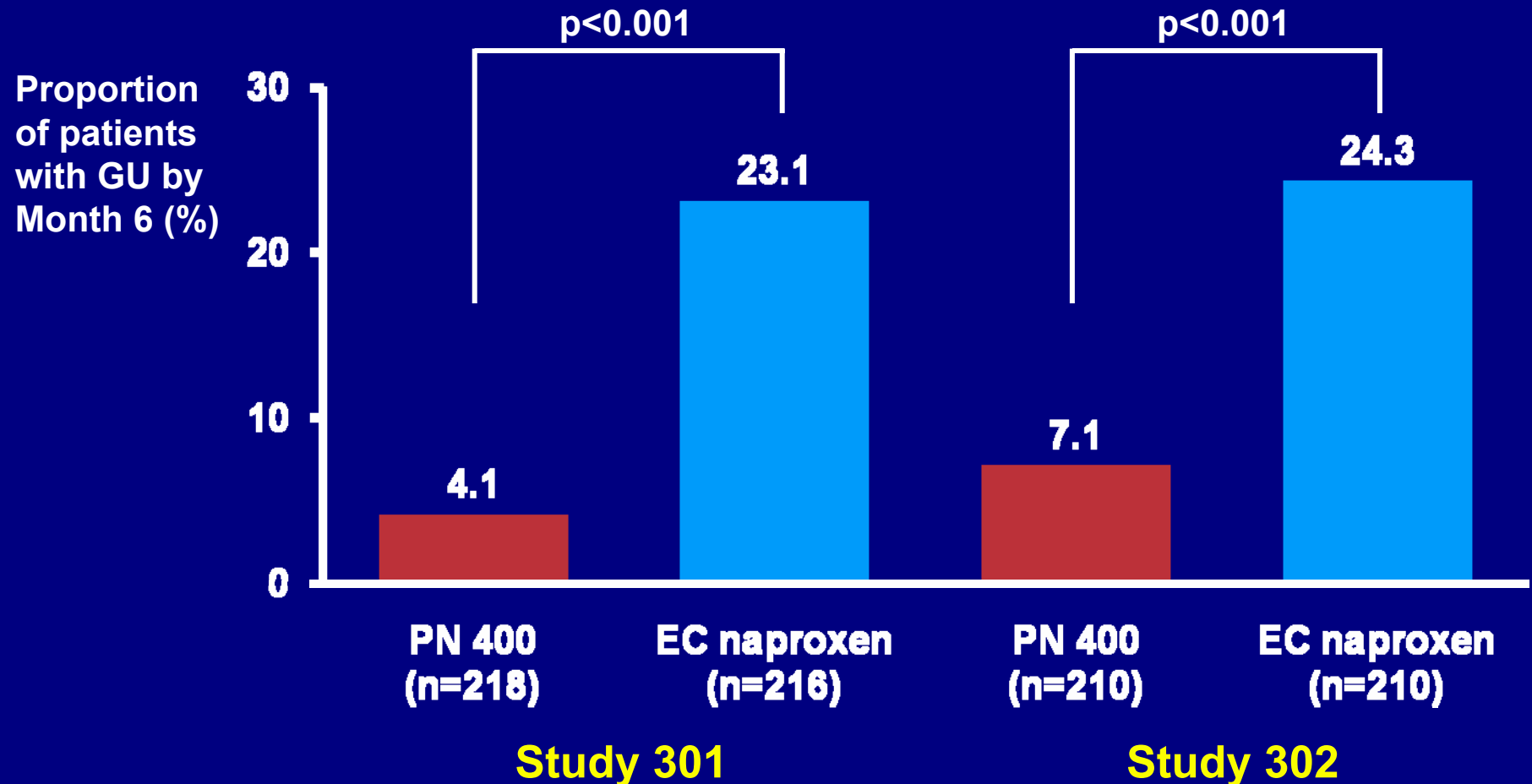


ITT, intent-to-treat population (received ≥1 dose of study drug and had no ulcer at screening)

Patient demographics and baseline clinical features

	Study 301		Study 302	
	PN 400 (n=218)	EC naproxen (n=216)	PN 400 (n=210)	EC naproxen (n=210)
Age (years), mean (range)	60.8 (30-90)	61.9 (43-90)	59.6 (27-85)	59.4 (29-82)
LDA use at randomization, n (%)	53 (24.3)	51 (23.6)	46 (21.9)	51 (24.3)
Indication for NSAID use				
Osteoarthritis	172 (78.9)	186 (86.1)	173 (82.4)	166 (79.0)
Rheumatoid arthritis	22 (10.1)	8 (3.7)	11 (5.2)	9 (4.3)
Other	53 (24.3)	38 (17.6)	48 (22.9)	59 (28.1)
Sex, n (%)				
Female	150 (68.8)	149 (69.0)	132 (62.9)	142 (67.6)
Race, n (%)				
White	184 (84.4)	181 (83.8)	183 (87.1)	190 (90.5)
Black	27 (12.4)	32 (14.8)	27 (12.4)	17 (8.1)
Other	7 (3.2)	3 (1.4)	1 (0.5)	3 (1.4)
Ulcer Hx within previous 5 years, n (%)	15 (6.9)	13 (6.0)	18 (8.6)	23 (11.0)

Cumulative incidence of GUs



Based on the ITT population with last observation carried forward for patients who discontinued prior to scheduled endoscopy at Month 6

Common treatment-emergent AEs

	Study 301		Study 302	
	PN 400 (n=218)	EC naproxen (n=216)	PN 400 (n=210)	EC naproxen (n=210)
Patients with ≥ 1 AE, n (%)	170 (78.0)	176 (81.5)	160 (76.2)	174 (82.9)
Most common AEs*, n (%)				
Erosive gastritis	45 (20.6)	81 (37.5)	38 (18.1)	81 (38.6)
Erosive duodenitis	4 (1.8)	30 (13.9)	5 (2.4)	20 (9.5)
Gastritis	39 (17.9)	28 (13.0)	34 (16.2)	32 (15.2)
Dyspepsia	36 (16.5)	65 (30.1)	41 (19.5)	49 (23.3)

*AEs reported by $\geq 10\%$ of patients in either treatment group from either study

Least-squares mean change from baseline in SODA scores after 6 months

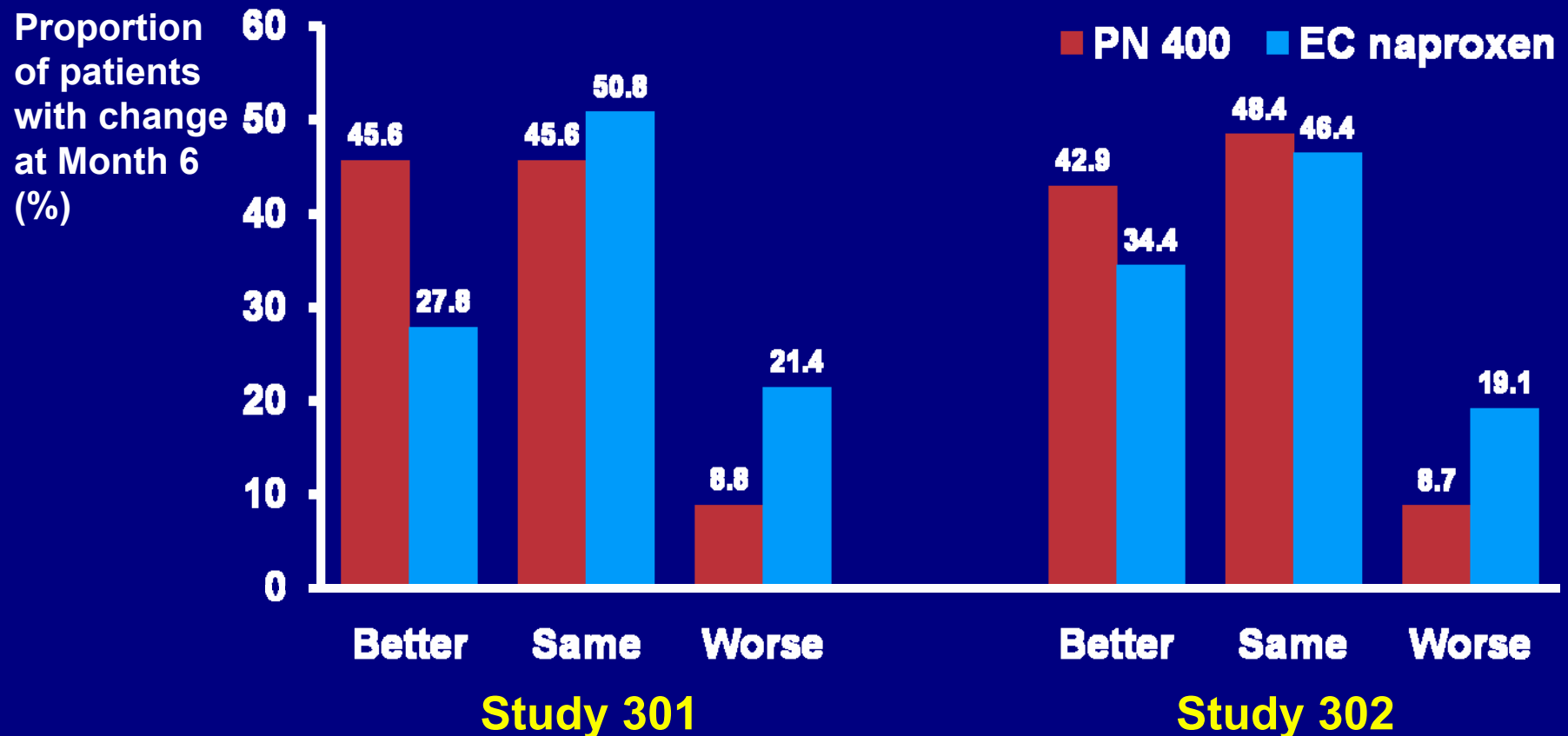
	Study 301			Study 302		
	PN 400 (n=218)	EC naproxen (n=216)	p	PN 400 (n=210)	EC naproxen (n=210)	p
Pain intensity [†]	-5.51	-0.15	<0.001	-2.64	0.09	0.004
Non-pain symptoms [†]	-2.16	-0.47	<0.001	-1.11	0.11	<0.001
Satisfaction [‡]	3.35	0.87	<0.001	1.88	0.47	0.003

[†]A negative value for LS mean change implies improvement

[‡]A positive value for LS mean change implies improvement

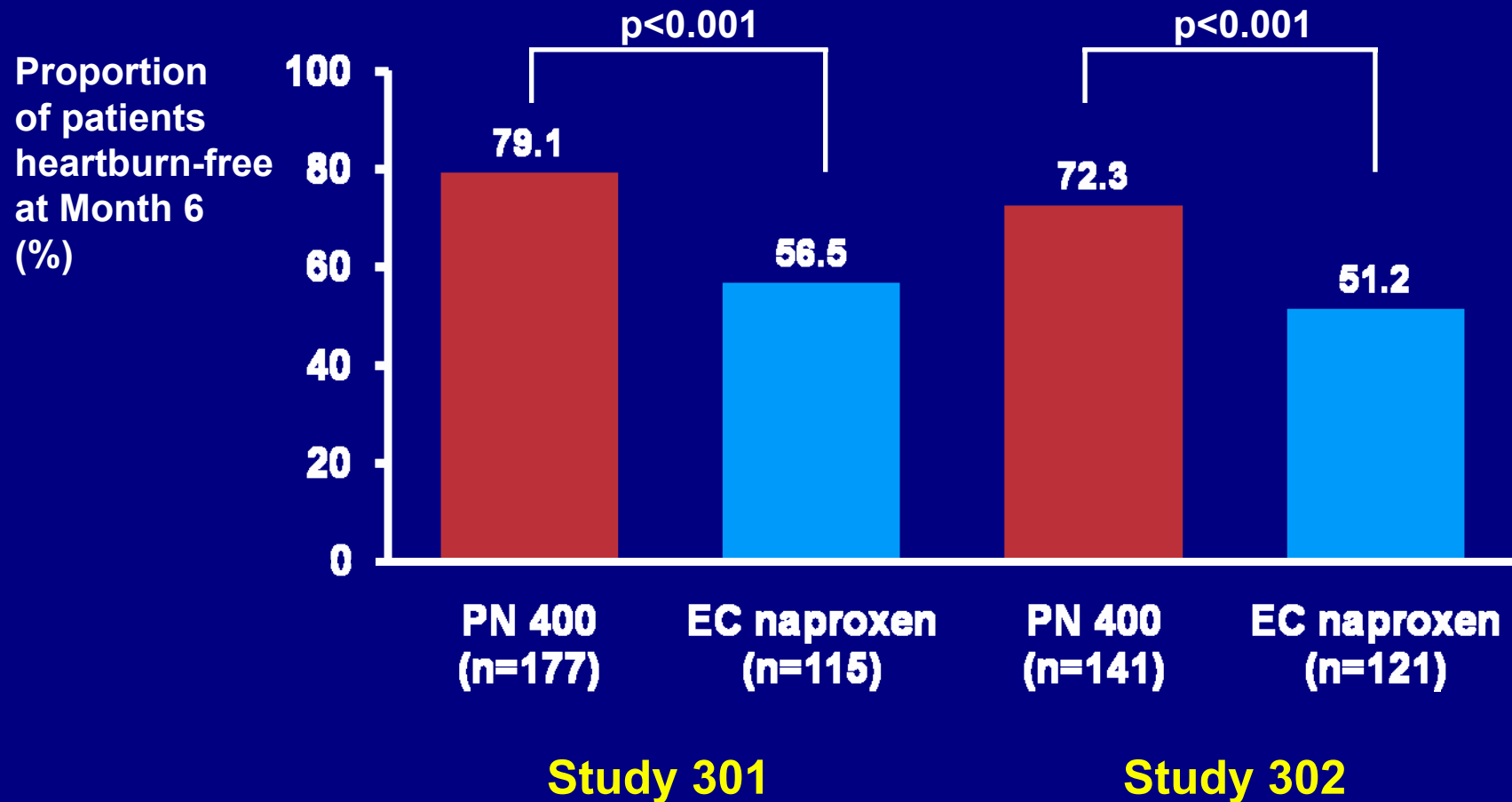
Last observation was carried forward where scores were unavailable at Month 6

Change in OTE-DP since start of treatment



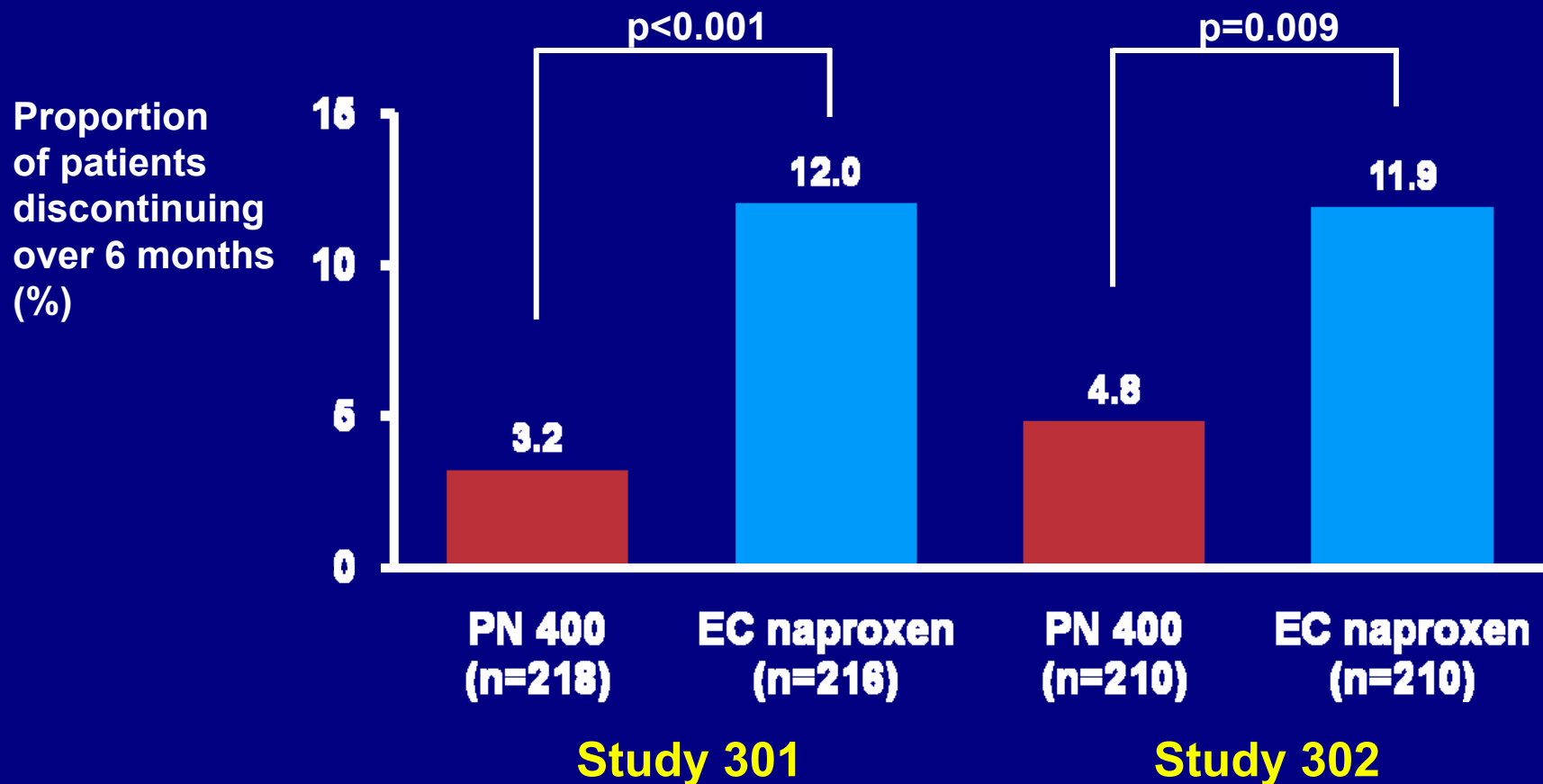
Based on a Wilcoxon rank-sum test comparing the distribution of OTE-DP responses, PN 400 was associated with significantly greater improvement relative to EC naproxen in Study 301 ($p < 0.001$) and Study 302 ($p = 0.017$)

Heartburn-free patients



Based on patients with heartburn assessment responses at both baseline and Month 6

Discontinuations due to NSAID-associated UGI AEs* or DUs



*Pre-defined endoscopic and symptomatic findings

Conclusions

- **Significantly reduced incidence of NSAID-associated GUs in at-risk patients**
- **Fewer UGI symptoms, including dyspepsia**
- **Improved UGI tolerability (SODA and OTE-DP)**
- **These data *may* offer an explanation for a lower rate of discontinuations due to UGI AEs and/or DUs**

Our data suggest that optimizing adherence to gastroprotection may improve NSAID tolerability and may result in sustained use