Scope of the Phase IIb/III OA Efficacy Program

	6 Week	1 Year
Number of Studies	**4**	**2**
Patients Randomized		
Total	**2312**	**1477**
Placebo	340	NA
Rofecoxib 12.5 mg	725	490
Rofecoxib 25 mg	662	489
NSAID	585	498

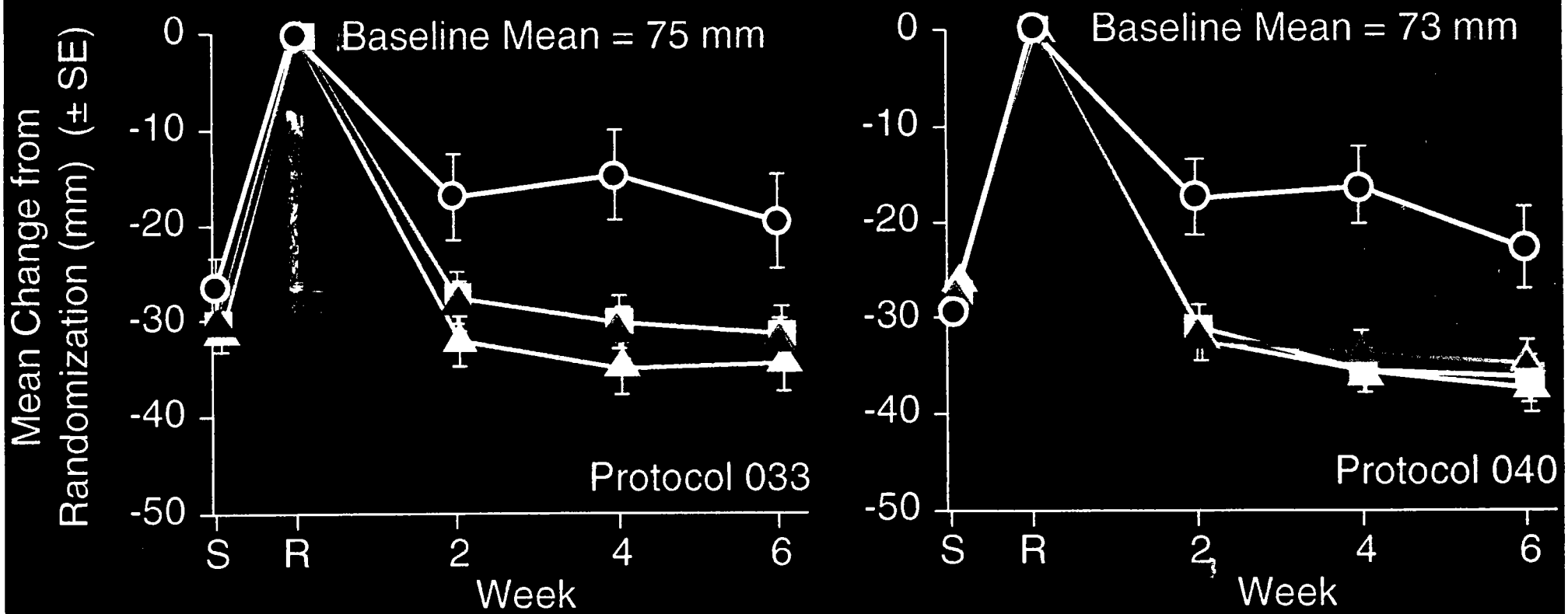
Demographics of Patients with OA Phase III Efficacy Studies

- All patients met clinical and radiographic criteria for OA
- All studies enrolled patients with knee or hip as the primary study joint
- 89% regular users of NSAIDs whose pain worsened upon discontinuation
- 11% routine acetaminophen users with OA symptoms at 2 visits
- Average duration of OA: 10 years
- Average age: 64 years (range 38 to 95 years)

Primary and Key Secondary Endpoints Rofecoxib OA Studies

- Primary endpoints
  - Walking pain (WOMAC)
  - Patient assessment of response to therapy
  - Investigator assessment of disease status
- Key secondary endpoints
  - Pain, stiffness, and physical function sub-scales (WOMAC)
  - Patient global assessment of disease status
  - Discontinuations due to lack of efficacy

OA Pain Walking on a Flat Surface
Rofecoxib 12.5 mg & 25 mg Once Daily

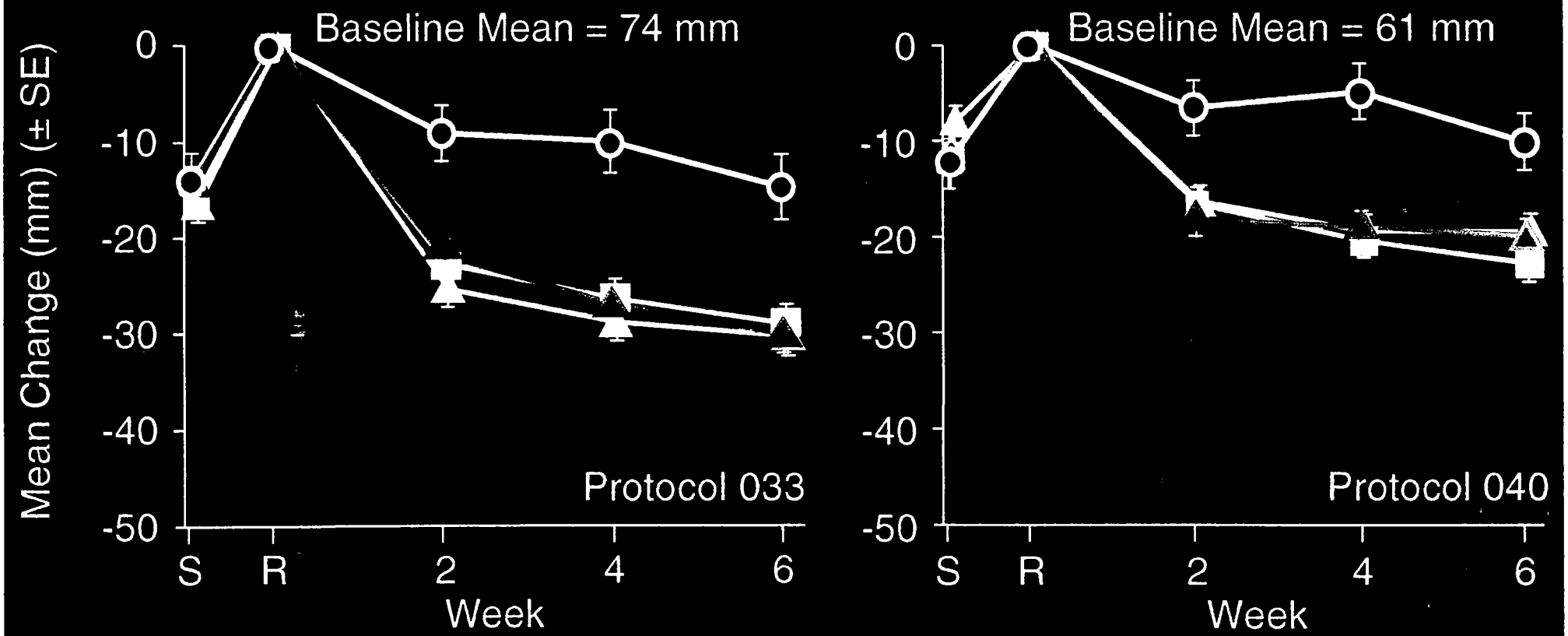


■ Rofecoxib 12.5 mg qAM	▲ Rofecoxib 25 mg qAM	Ibuprofen 800 mg TID	O Placebo
N=219,244	N=227,242	N=221,249	N=69,74

$p < 0.001$, all groups compared with placebo.

Protocol 033/040

Rofecoxib Relieves OA Joint Stiffness, Upon Awakening 12.5 mg & 25 mg Once Daily qAM

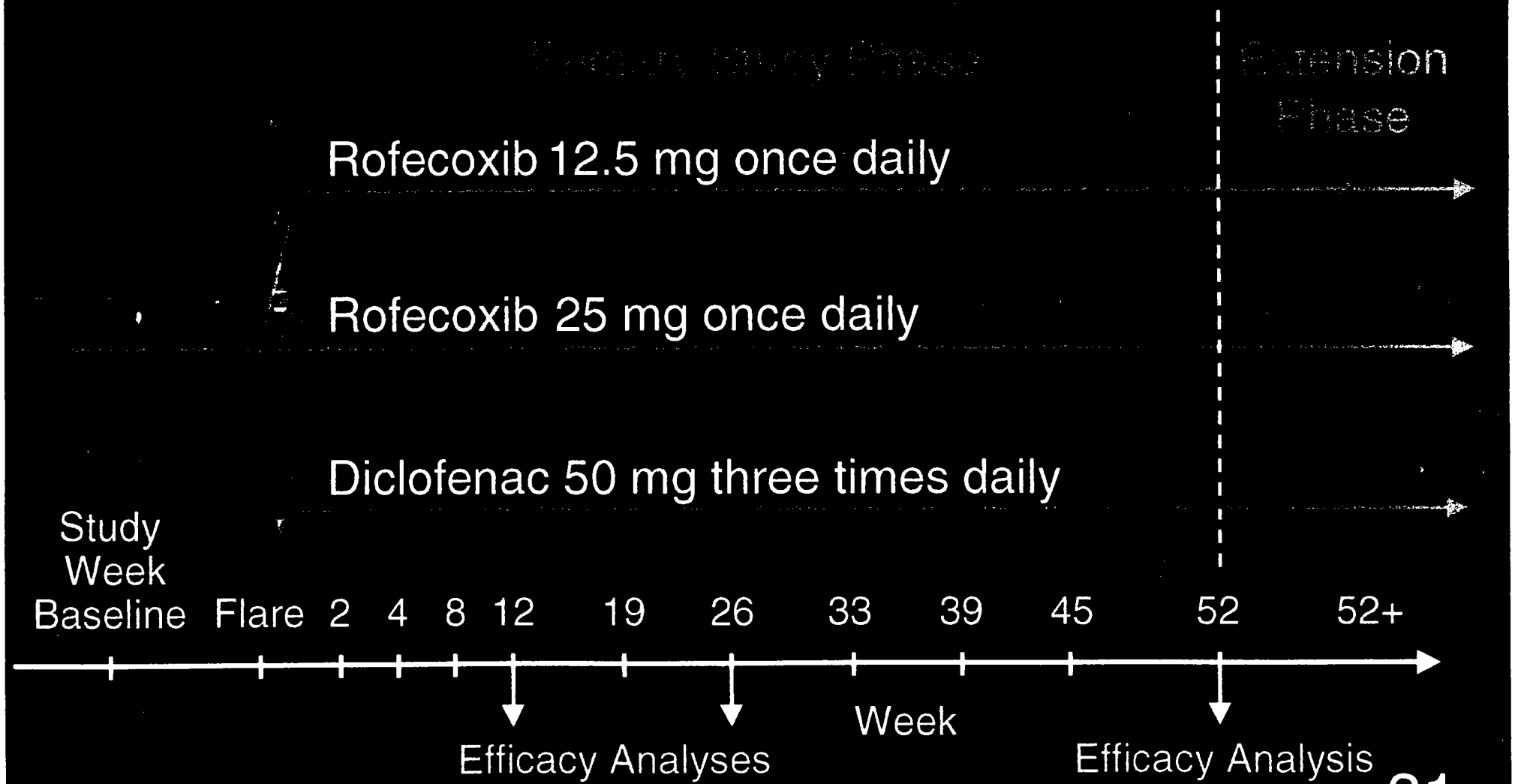


■ Rofecoxib 12.5 mg qAM N=219,244	▲ Rofecoxib 25 mg qAM N=227,242	Ibuprofen 800 mg TID N=221,249	○ Placebo N=69,74

$p < 0.001$, all groups compared with placebo.

Protocol 033, 040

One Year Phase III OA Efficacy Studies Plus Extensions
Study Schematic

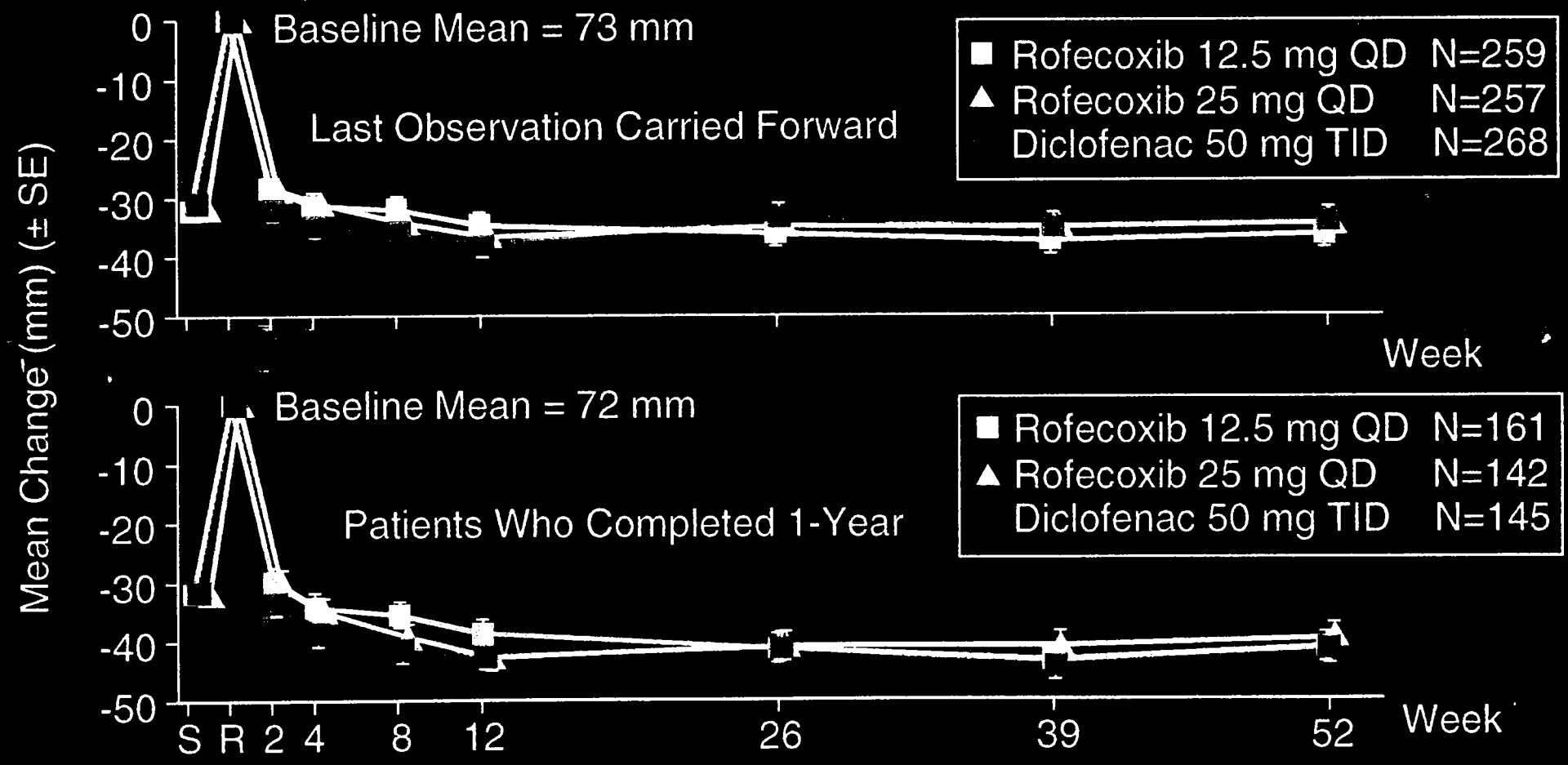


One Year Phase III OA Efficacy Studies
Patient Accounting

	Rofecoxib				Diclofenac	
	12.5 mg		25 mg		150 mg	
Number of Patients Randomized	259		257		268	
	N	(%)	N	(%)	N	(%)
Completed	161	(62)	142	(55)	145	(54)
Discontinued	98	(38)	115	(45)	123	(46)
Adverse Experience	38	(15)	34	(13)	55	(21)
Lack of Efficacy	36	(14)	56	(22)	43	(16)
Other	24	(9)	25	(10)	25	(9)

Protocol 035

Long Term Efficacy in OA - Rofecoxib 12.5 mg & 25 mg QD
OA Pain Walking on a Flat Surface



$p < 0.001$, all groups compared to baseline.

Protocol 035

Consistency of Response
Pain, Walking on a Flat Surface (WOMAC)

	Rofecoxib 12.5 mg		Rofecoxib 25 mg	
6 Weeks:				
Protocol 033	N=190	-34	N=201	-36
Protocol 040	N=219	-38	N=221	-38
12 Weeks:				
Protocol 034	N=197	-35	N=204	-35
Protocol 035	N=217	-36	N=204	-39
52 Weeks:				
Protocol 034	N=153	-38	N=162	-39
Protocol 035	N=166	-43	N=143	-41

Rationale for Doses Recommended for Osteoarthritis

Primary dose: Rofecoxib 12.5 mg once daily

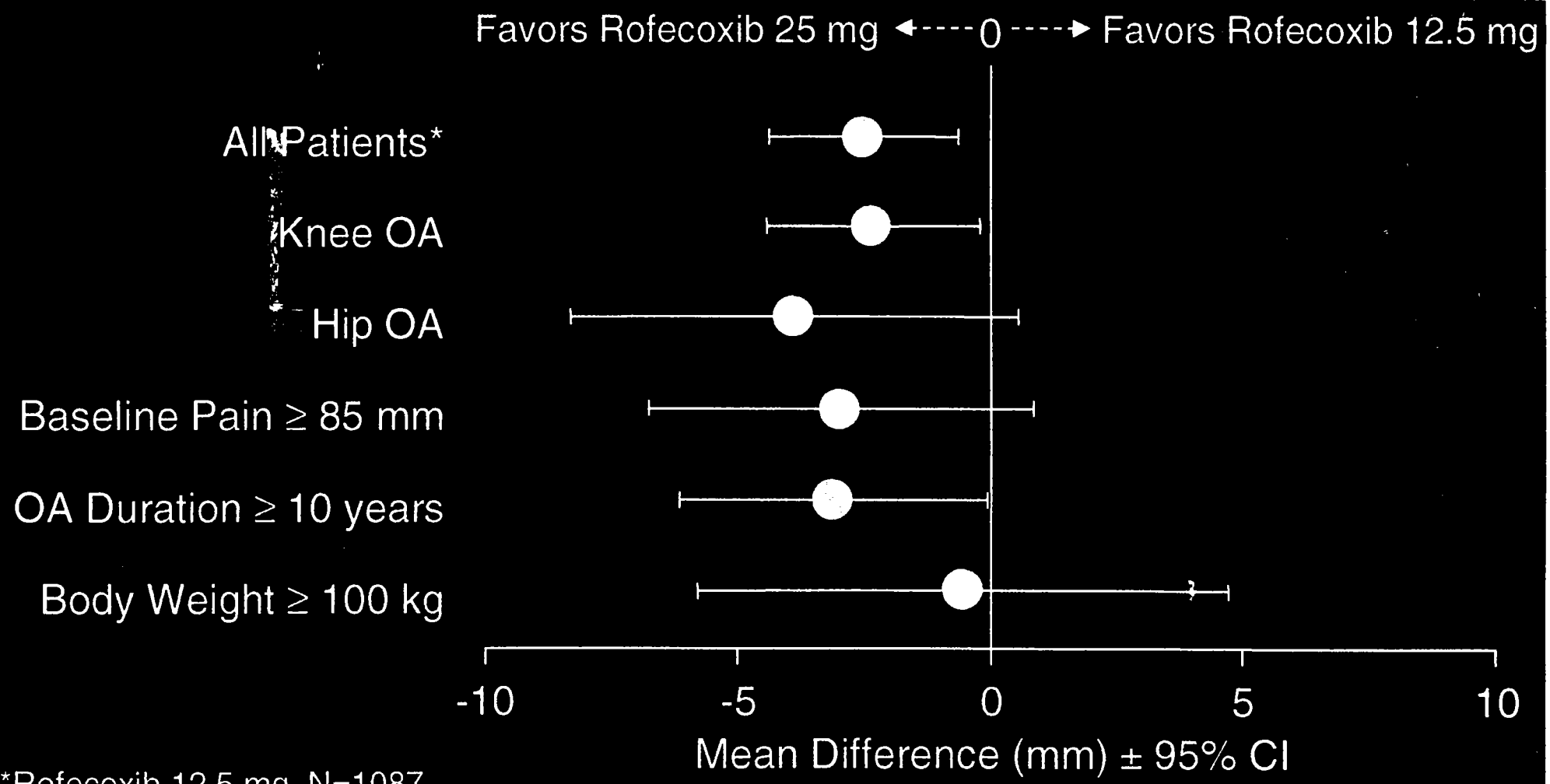
Some patients may receive additional benefit from 25 mg

Optimal Doses Rofecoxib 12.5 and 25 mg QD Two 6-Week Phase II Dose Ranging Studies

Treatment	Protocol	Patient Global Response to Therapy (0 to 4 Scale) Mean Difference from Placebo	Lower Extremity Edema % Patients with ≥ 1 AE
Placebo			
	Protocol 029 N=145		0.7%
Rofecoxib			
5 mg	Protocol 029 N=149	0.8	2.7%
12.5 mg	Protocol 029 N=144	1.0	2.1%
25 mg			
	Protocol 029 N=137	1.1	2.2%
50 mg	Protocol 029 N=97	1.3	5.2%
125 mg			

Rationale for Including Rofecoxib 25 mg Once Daily

Pain Walking on a Flat Surface: Combined OA Studies



*Rofecoxib 12.5 mg N=1087
Rofecoxib 25 mg N=1075

Protocols 029, 033, 034, 035, 040 Combined

Osteoarthritis Efficacy Summary Rofecoxib 12.5 mg & 25 mg Once Daily

- Clinically effective in the treatment of osteoarthritis
- Efficacy statistically equivalent to:
  - Diclofenac 50 mg three times daily
  - Ibuprofen 800 mg three times daily
- Sustained efficacy for 24 hours with once daily dosing
- Efficacy maintained with chronic treatment for > 1 year
- Recommended doses:
  - Primary dose 12.5 mg, some patients may receive additional benefit from 25 mg

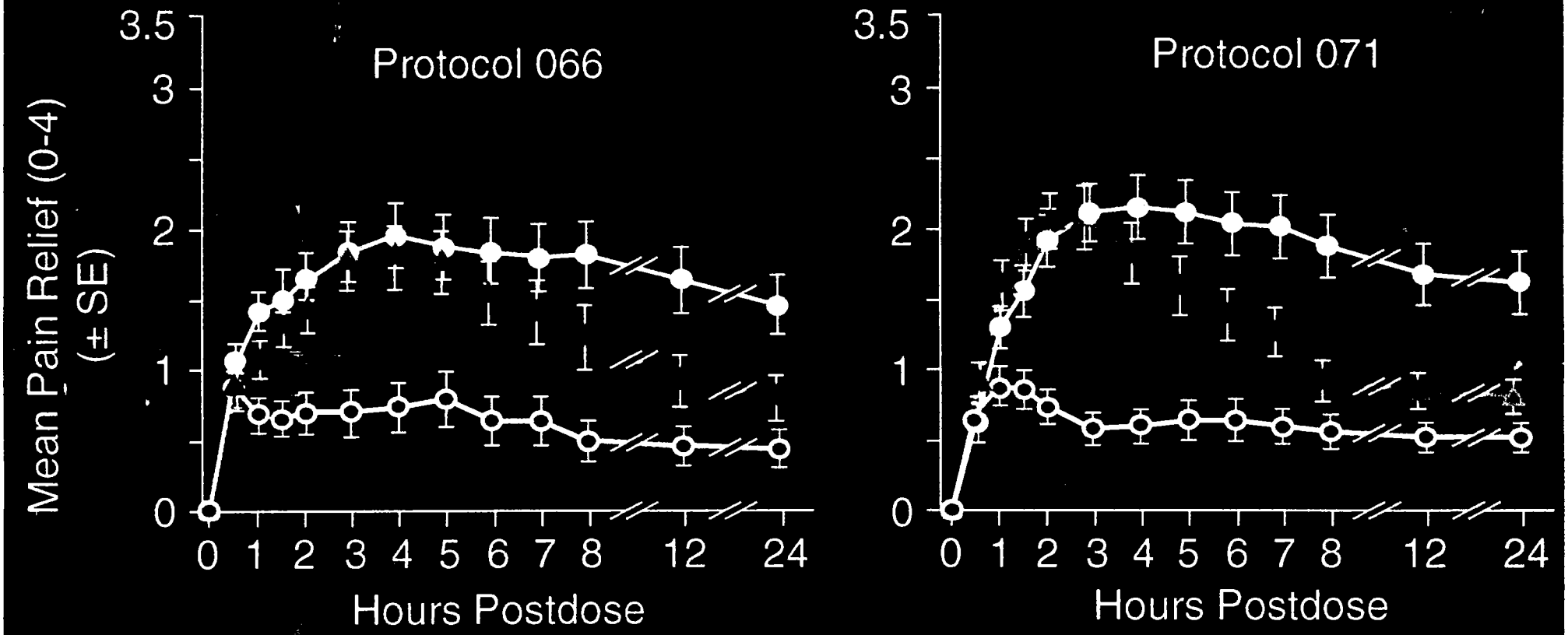
Efficacy in Analgesia

- Three validated models of pain
  - Dental surgery - pain following removal of molars
  - Primary dysmenorrhea - painful cramps with no other identified etiology
  - Orthopedic surgery - pain following total hip or knee replacement
- Single dose data
- Multiple dose data

Scope of Analgesia Program

	Dental Surgery Pain 1 day study	Primary Dysmenorrhea 3 day study	Orthopedic Surgery Pain 5 day study
Number of Studies	**5**	**3**	**1**
Patients Randomized			
Total	**1061**	**272**	**218**
Placebo	219	227	53
Rofecoxib	631	261	110
NSAID	211	230	55

Dental Surgery Pain
Pain Relief Over Time



	● Rofecoxib 50 mg	Ibuprofen 400 mg	○ Placebo
Protocol 066	N=50	N=51	N=50
Protocol 071	N=50	N=52	N=50

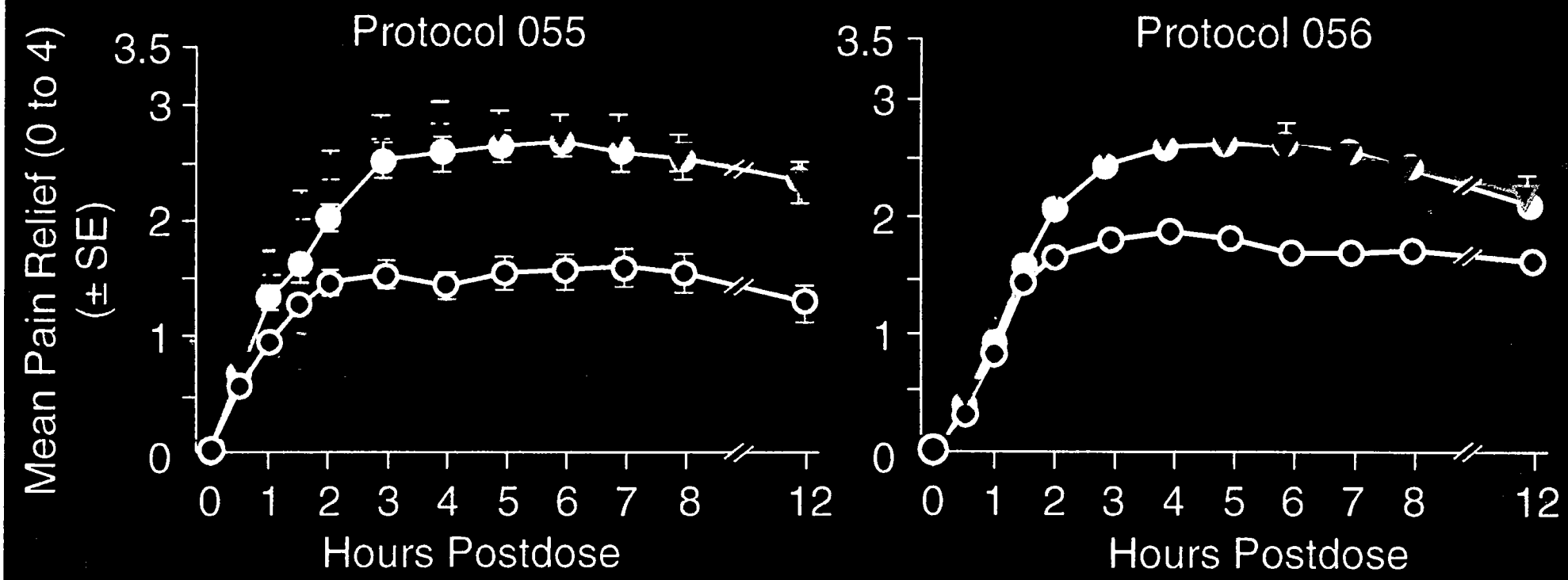
$p < 0.001$ rofecoxib compared with placebo.

Dental Surgery Studies – Duration of Action
Time to Rescue Medication

	Median Time to Rescue (Hours)		
	Placebo	Ibuprofen 400 mg	Rofecoxib 50 mg
Protocol 066	6.4 N=17/50 (34%)	9.3 N=32/51 (63%)	>24 * N=32/50 (64%)
Protocol 071	3.1 N=12/50 (24%)	7.0 N=35/52 (67%)	23.6 * N=37/50 (74%)

* $p < 0.001$ compared with placebo.

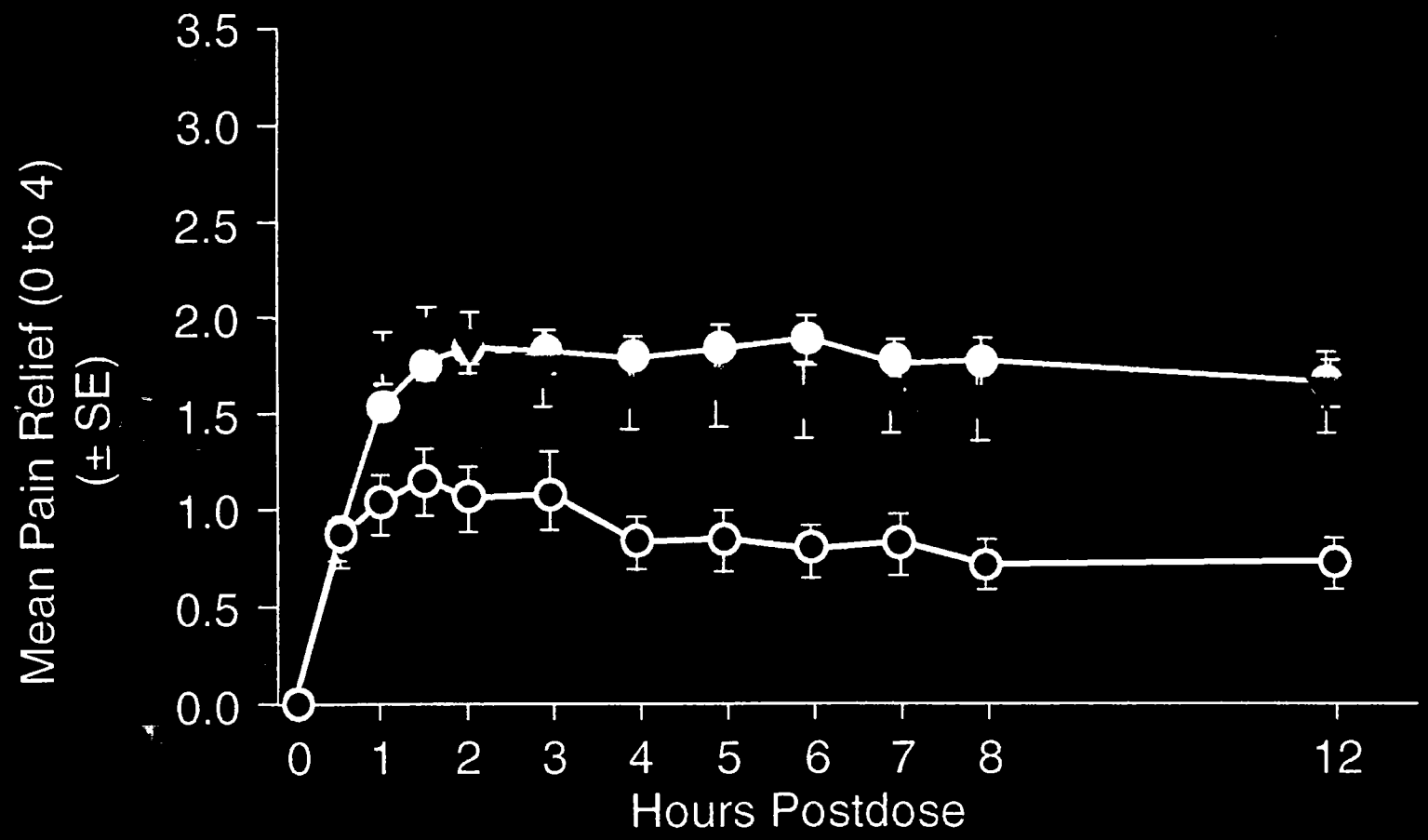
Efficacy in Primary Dysmenorrhea
Rofecoxib 50 mg Initial Dose



	● Rofecoxib 50 mg	Naproxen Sodium 550 mg	○ Placebo
Protocol 055	N=60	N=59	N=60
Protocol 056	N=118	N=122	N=118

$p < 0.002$ rofecoxib compared with placebo.

Efficacy in Orthopedic Surgery Pain
Rofecoxib 50 mg Day 1

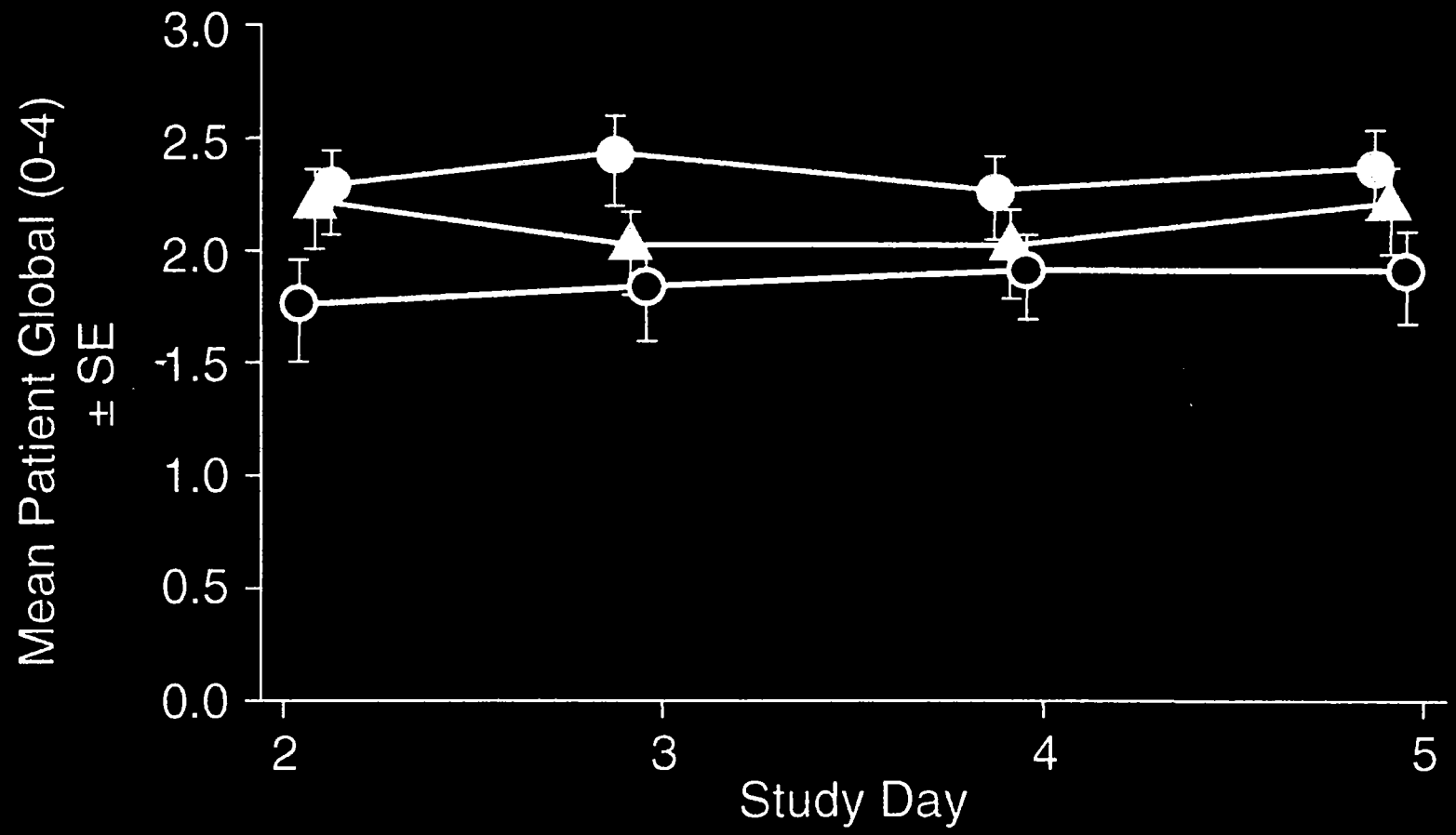


● Rofecoxib 50 mg N=110 Naproxen Sodium 550 mg N=55 ○ Placebo N=53

$p < 0.001$ rofecoxib compared with placebo.

Protocol 072

Multiple Dose Efficacy Orthopedic Surgery Pain
Patient's Global Evaluation of Study Therapy Days 2 to 5



▲ Rofecoxib 25 mg N=56 ● Rofecoxib 50 mg N=54 ○ Placebo N=53

p = 0.041 rofecoxib 50 mg compared with placebo.

Protocol 072

Rofecoxib: Efficacy in Analgesia

- Rofecoxib efficacy confirmed in all three types of pain
  - Dental surgery - Day 1 over 24 hours, single dose
  - Dysmenorrhea -Day 1 over 24 hours
  - Orthopedic surgery -Day 1 over 12 hours (last timepoint measured on Day 1), once daily for 5 days
- Rapid onset of action (~45 minutes)
- 24 hour duration of action, consistent with once daily dosing
- Recommended dosing (1 to 5 day studies)
  - Primary dose 50 mg once daily

    After the first dose, some patients may receive relief from acute pain with 25 mg once daily

Rofecoxib
Efficacy Conclusions

- A COX-2 specific inhibitor
- Efficacy in osteoarthritis 12.5 and 25 mg once daily
  - Clinically and statistically equivalent to Ibuprofen 800 mg TID and Diclofenac 50 mg TID
- Efficacy in analgesia 50 mg once daily
  - Similar to Ibuprofen 400 mg and Naproxen sodium 550 mg
- For the treatment of osteoarthritis and relief of acute pain sustained efficacy for 24 hours following a single daily dose

Rofecoxib
Gastrointestinal Safety

Evaluation of Rofecoxib Human Gastrointestinal Safety

Dr. Thomas Simon