

**FDA
ONCOLOGIC DRUGS ADVISORY
COMMITTEE MEETING**

December 14, 1999

PRESENTATION

**CELEBREX CAPSULES
(Celecoxib)**

Familial Adenomatous Polyposis (FAP)

NDA 21-156

**Richard N. Spivey, Pharm.D., Ph.D.
Vice President of Worldwide
Regulatory Affairs
Searle**

CELEBREXTM
(Celecoxib)
Capsules

Indication

- **Celebrex is indicated for the reduction and regression of adenomatous colorectal polyps in Familial Adenomatous Polyposis patients**

Agenda

Introduction

Dr. Richard Spivey (Searle)

Background

**Dr. Philip Needleman (Searle)
Dr. Gary Kelloff (NCI)**

Preclinical

Dr. Jaime Masferrer (Searle)

Clinical

- **Disease Background**
- **Efficacy Data**
- **Safety Data/Follow-up Plan**

Dr. Bernard Levin (MDACC)

Dr. Ernest Hawk (NCI)

Dr. Gary Gordon (Searle)

Conclusions

Dr. Philip Needleman (Searle)

Presentation

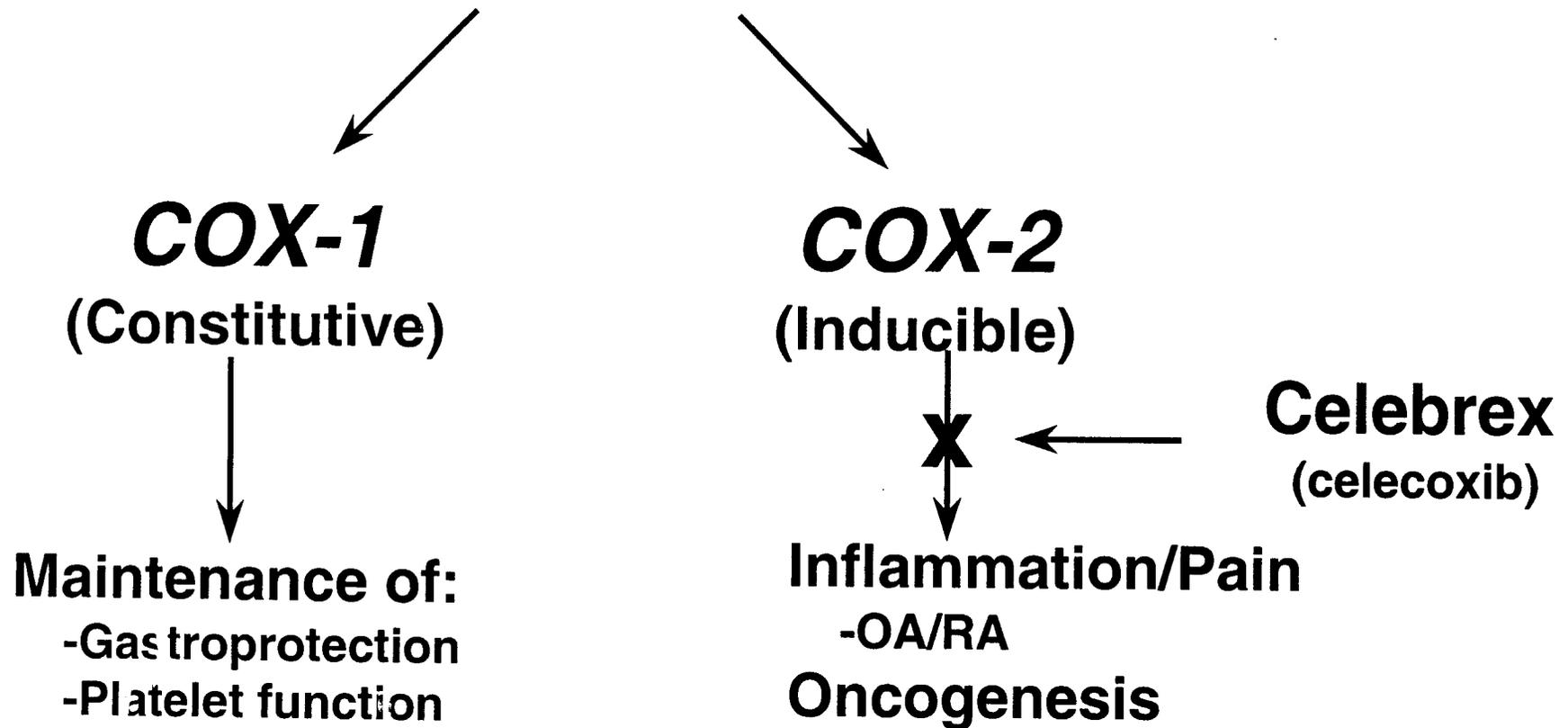
- **Celecoxib, 400 mg BID, is safe and effective for the reduction and regression of adenomatous colorectal polyps in patients with FAP, in conjunction with usual care**
- **Celecoxib shows a consistent benefit throughout the GI tract**
- **Celecoxib is well tolerated in patients with FAP**

COX-2 and Celecoxib

Philip Needleman, Ph.D.
Co-President, Searle
Chief Scientist, Monsanto

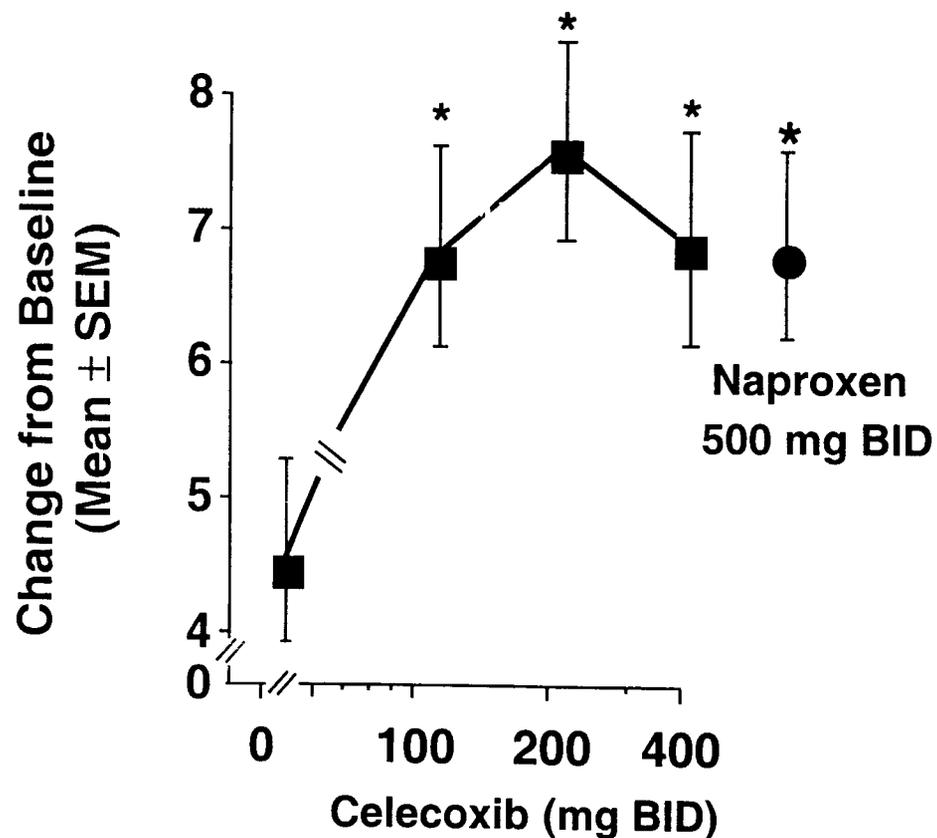
COX-2 Inhibitors: Mechanism Based Drug Targeting

Arachidonic Acid

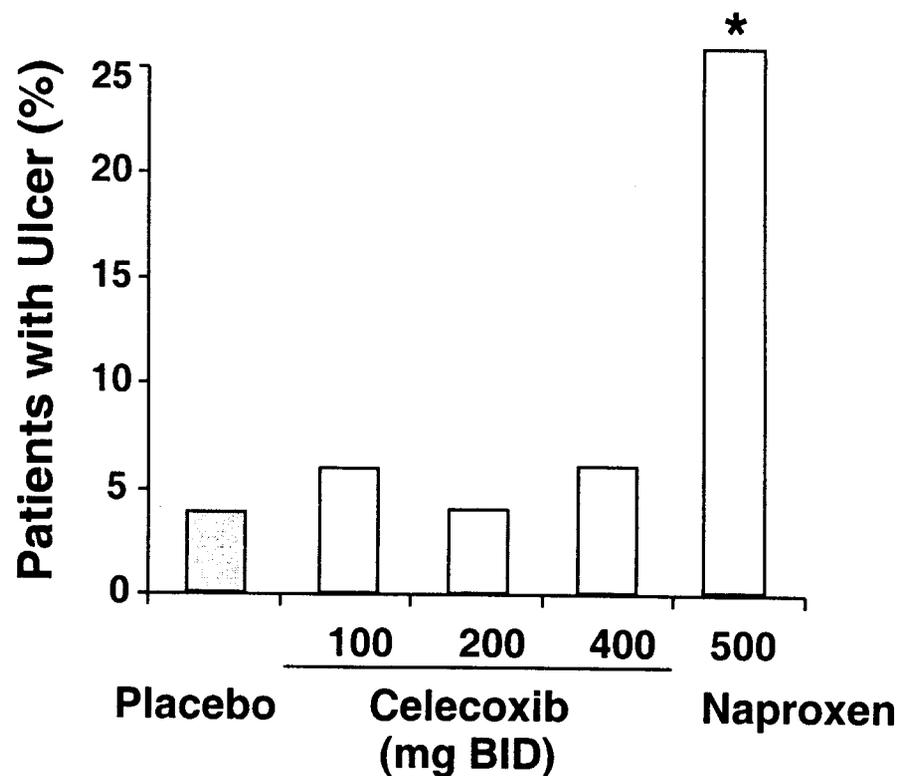


Clinical Efficacy of Celecoxib in RA Patients

Reduction in Number of Swollen Joints



Incidence of Gastroduodenal Ulcers



* Significantly different from 0 mg; $P \leq 0.05$

* $P < 0.001$ vs other treatments

Simon LS, et al. JAMA 282 20:1921-1928, 1999

Milestones in Searle / COX-2 Research

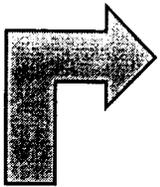
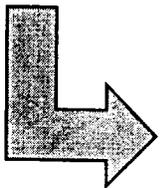
- 1990 Two Enzyme (COX-1/COX-2) Hypothesis
- 1995 Celecoxib trials initiated in arthritis and pain
- 1995 Celecoxib reduces incidence of colon cancer in animals
- 1996 Searle and NCI initiate study to test celecoxib efficacy in FAP patients
- 1998 Celebrex approved by the FDA for arthritis
- 1999 Celebrex can safely and effectively reduce and regress polyps in patients with FAP
- 1999-2000 Searle/NCI initiate celecoxib trials in SAP, actinic keratosis, Barrett's esophagus, and bladder cancer

FAP PATHOPHYSIOLOGY

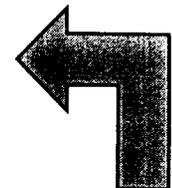
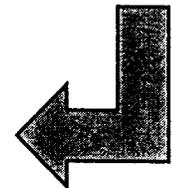
- Genetic basis of disease
- Adenoma-carcinoma sequence
- Serial endoscopic surveillance
- COX-2 overexpression
- Well-established preclinical models

NSAID CANCER PREVENTION

- Preclinical data
- Observational data
- Intervention data
- Safety concerns



NCI-CONTRACTED TRIAL OF CELECOXIB IN FAP



G. D. SEARLE

- COX-2 technology
- Celecoxib safety database
- Celecoxib preclinical data

FAP PATIENTS

- Unmet clinical need
- Limited cohort
- MDACC & St. Mark's registries

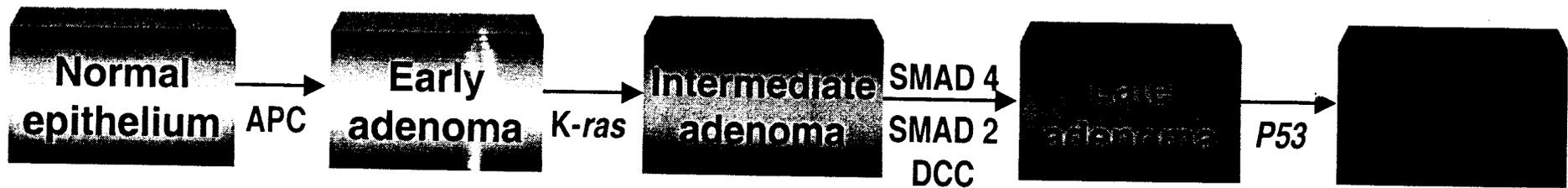
Celecoxib FAP Study

- **Largest controlled trial in FAP**
- **Accelerated review process granted by FDA under subpart H**
- **For use in conjunction with usual medical and surgical care of patients with FAP**

Colon Cancer Prevention

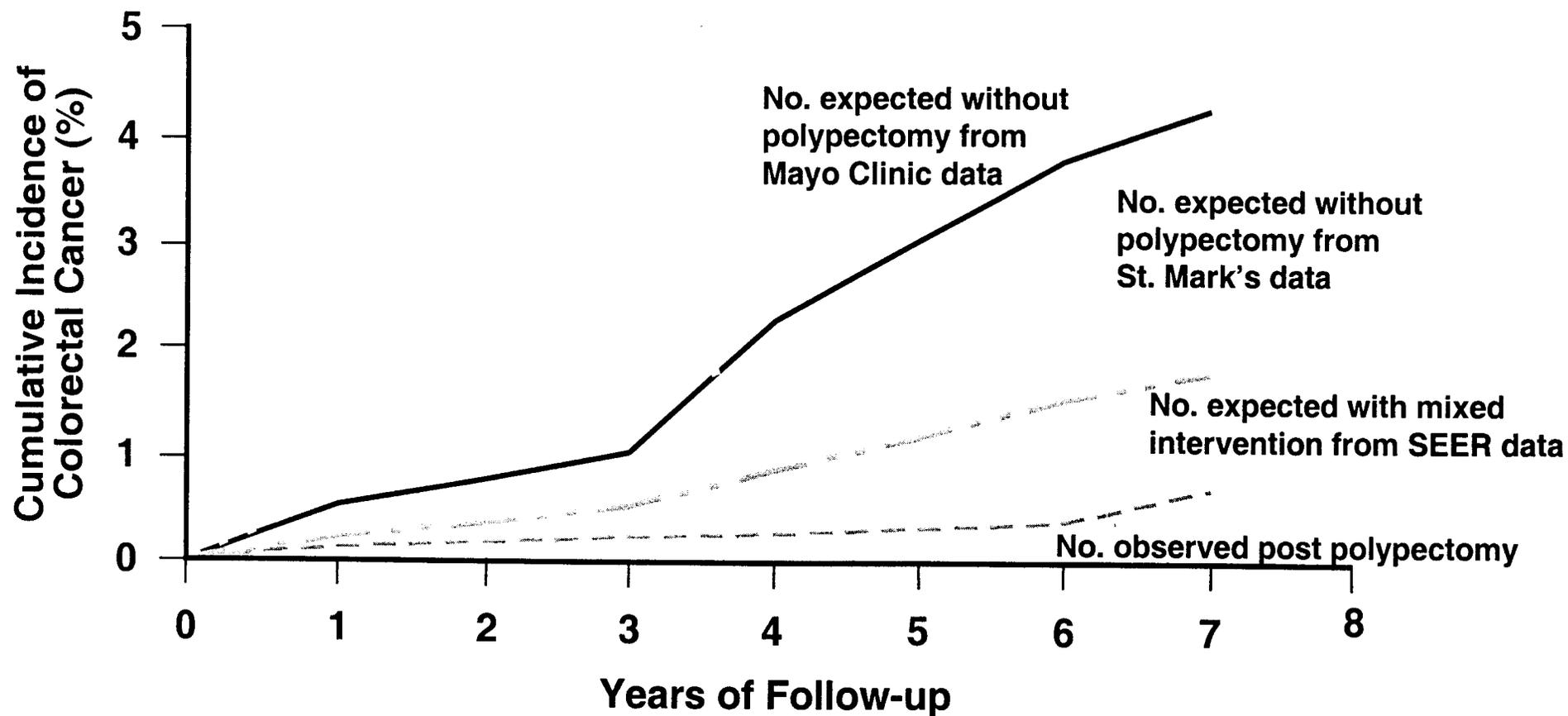
Gary Kelloff, M.D.
Chief, Chemopreventive Agent
Development Research Group
National Cancer Institute

Genetic Pathway in Colorectal Carcinogenesis



Adapted from: Ilyas et al., Eur. J. Cancer 35: 335–351, 1999

National Polyp Study: Validation of Adenomas as Surrogates for Colorectal Cancer

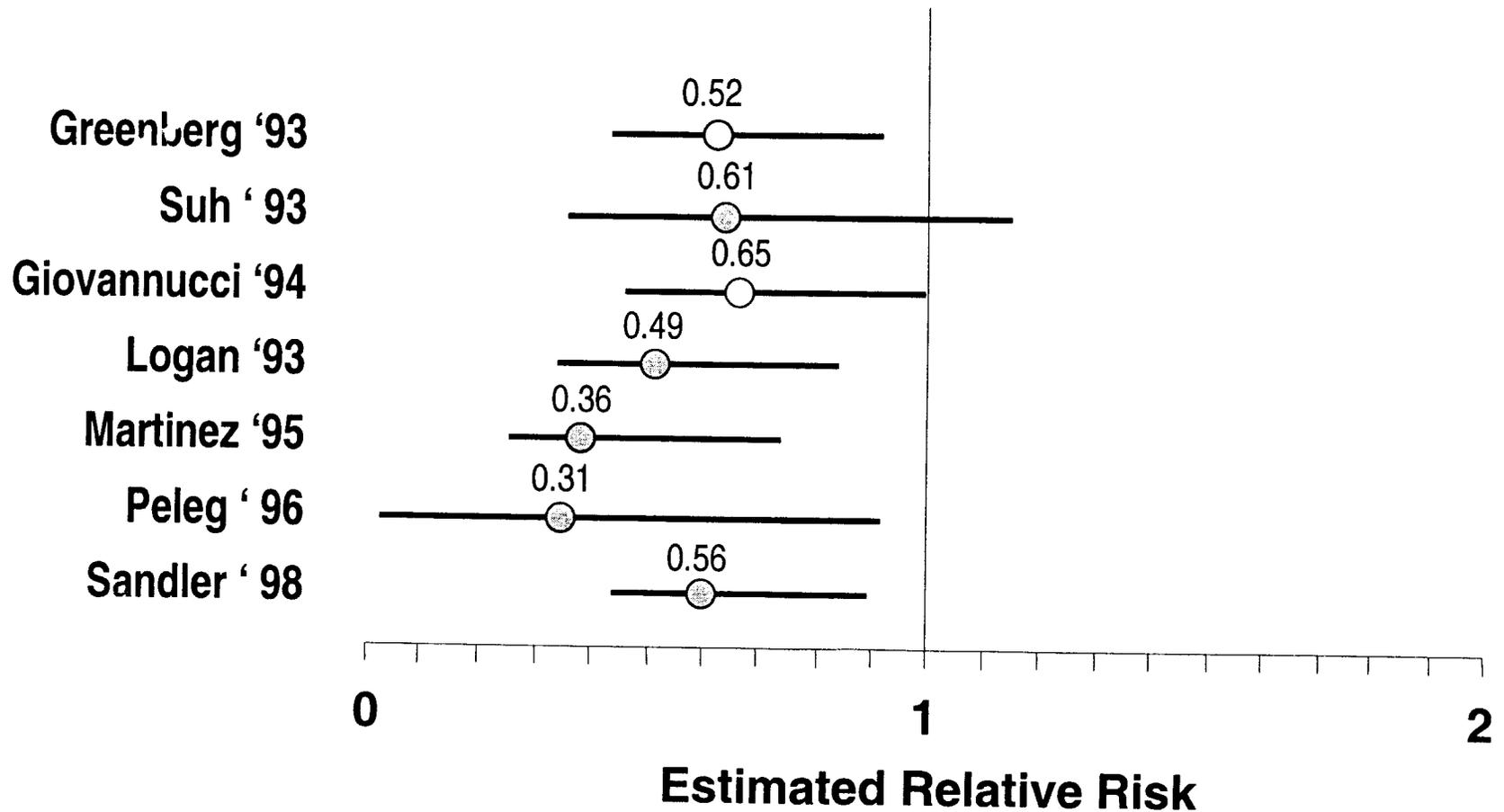


Winawer SJ, *et al.* N Engl J Med 329: 1977-1981, 1993

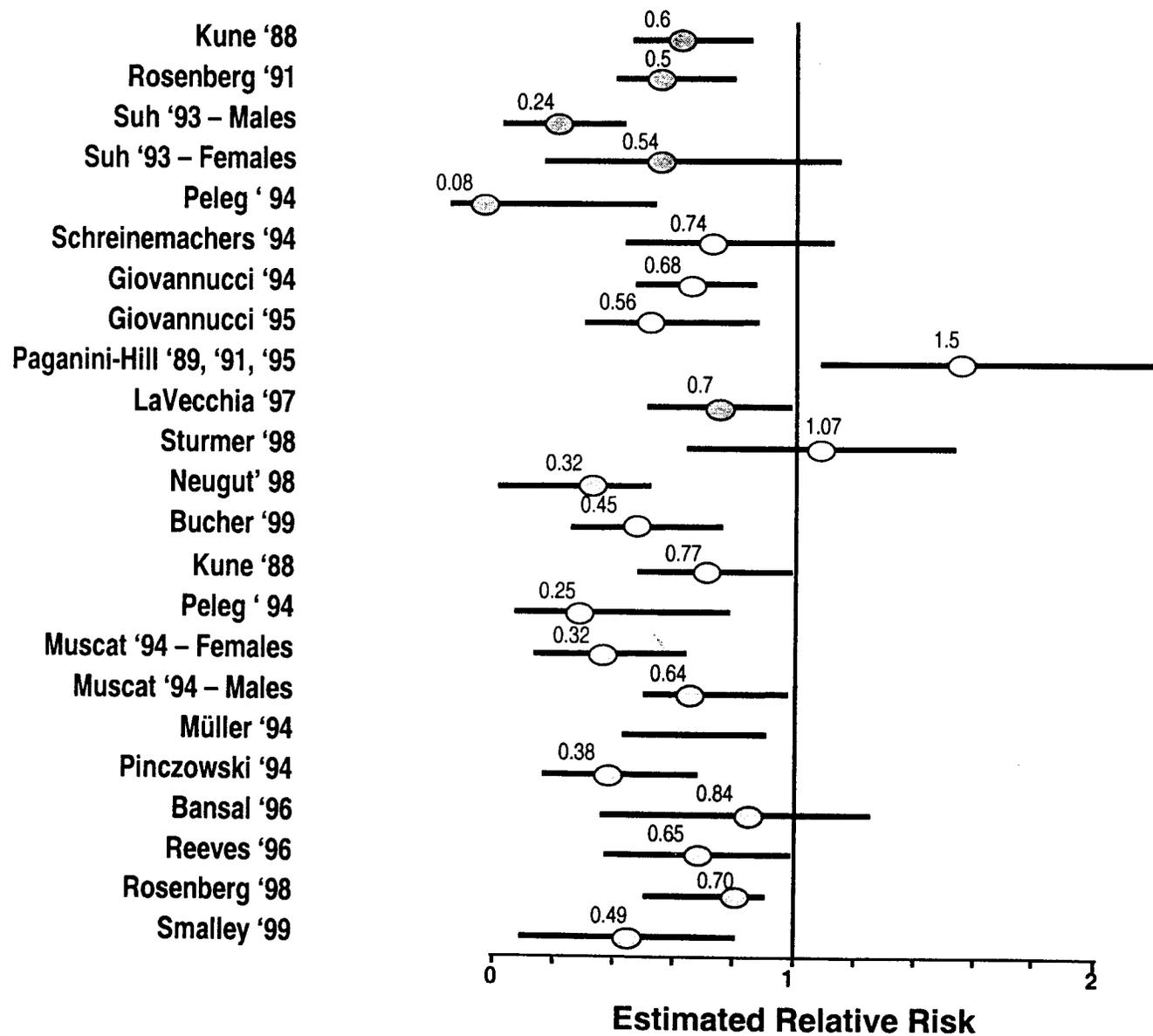
NSAIDS and Colorectal Cancer

- **Consistent effect in animal studies, human observation, and clinical intervention studies**
 - **Reduced incidence, multiplicity and size of tumors in animal models of colon cancer**
 - **Reduced incidence of adenomas, colon cancer and colon cancer deaths in NSAID users**

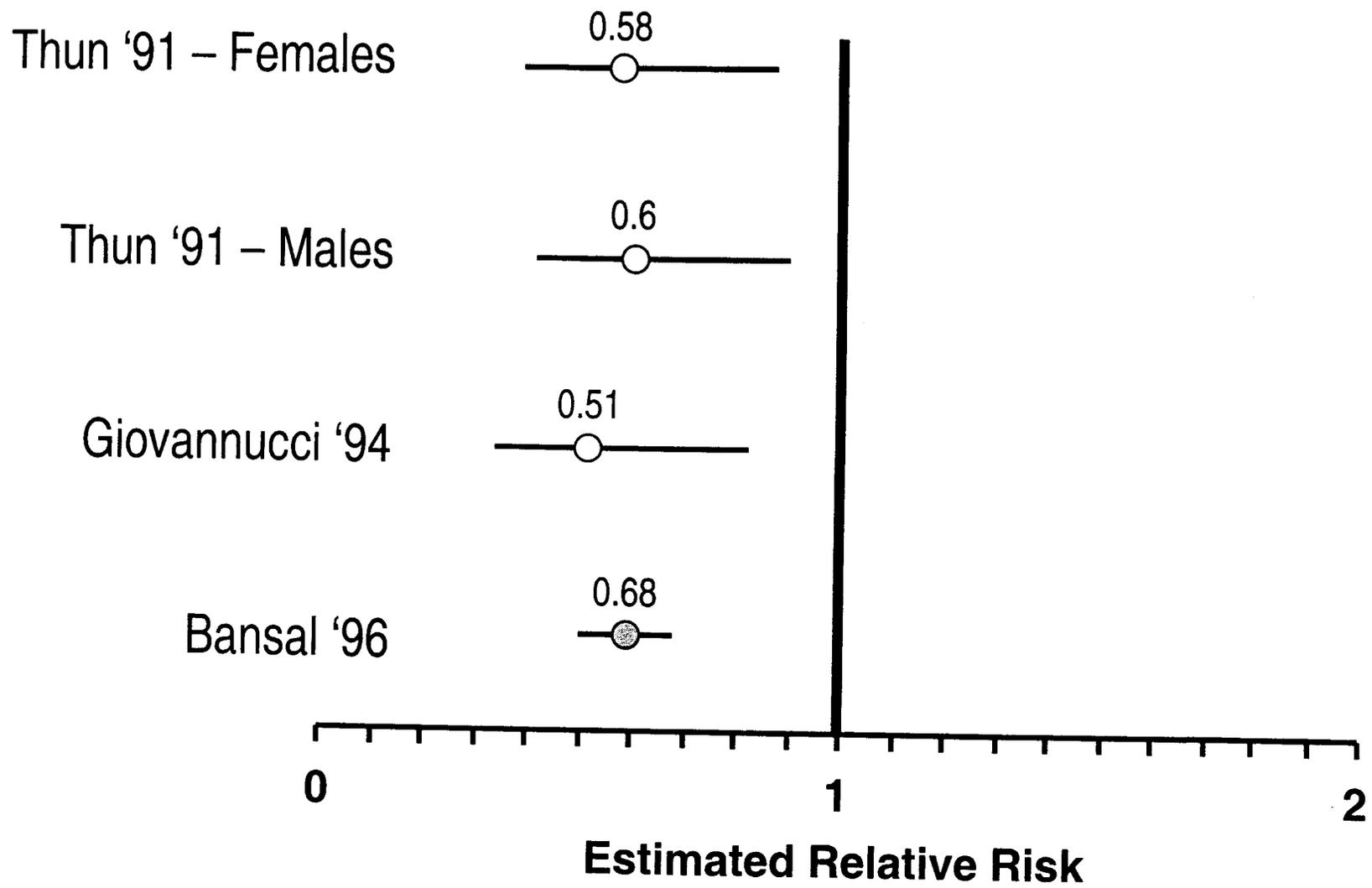
NSAID Use and Colorectal Polyp/Adenoma Incidence



NSAID Use and Colorectal Cancer Incidence



NSAID Use and Colorectal Cancer Mortality



NSAIDs in Colorectal Cancer—Epidemiological Efficacy

- **Reductions in**
 - **Adenoma incidence**
 - **Carcinoma incidence**
 - **Cancer-associated mortality**
- **Activity observed across cohorts**
 - **General population and at-risk subjects**
 - **Men and women, middle and older ages**
 - **Left- and right-sided lesions**
 - **Wide-ranging geographies (US, Europe, Australia)**
- **Extraordinarily consistent results**

Limitations of NSAIDs for Colorectal Cancer Prevention

- **Safety issues**
 - **GI ulcers/bleeds**
 - **Dyspepsia**
 - **Platelet effects**

NCI Interest in Celecoxib

- **NSAIDs impact colorectal carcinogenesis**
- **Safety of NSAIDs limits use**
- **Pre-clinical efficacy of celecoxib is at least comparable to NSAIDs**
- **Significantly better safety profile for celecoxib than NSAIDs**
- **Substantial potential of celecoxib for patient benefit**

Celecoxib Colon Cancer Preclinical Pharmacology

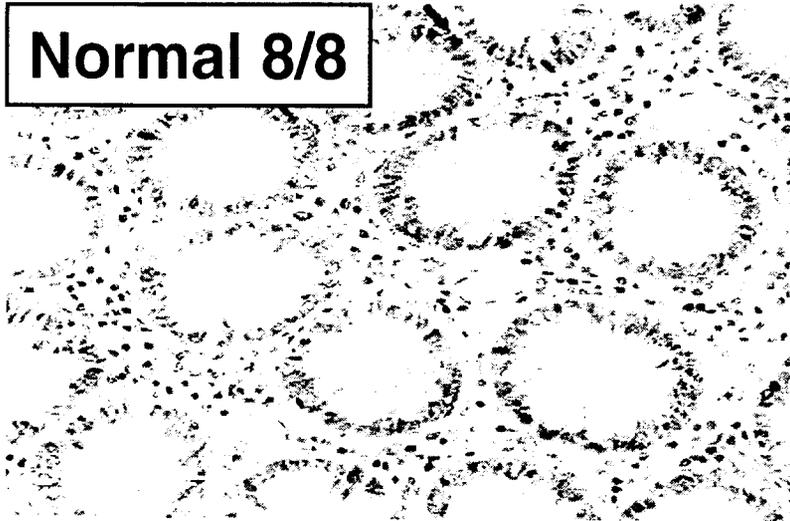
Jaime L. Masferrer, Ph.D.
COX-2 Cancer Project Leader
Group Leader Discovery Pharmacology
Searle/Monsanto

Scientific Rationale: Use of COX-2 Inhibitor in Cancer

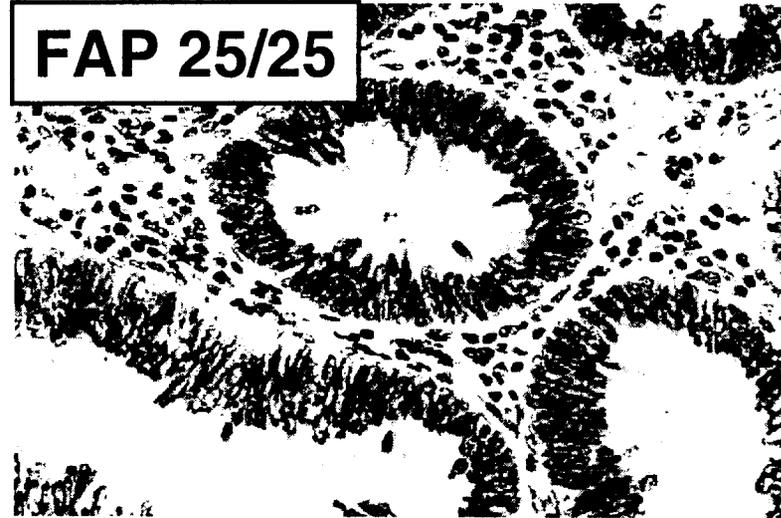
- **Epidemiology with NSAIDs**
- **COX-2 Expression in Human Tumors**
- **Animal Pharmacology**

COX-2 Is Expressed in All Stages of Human Colon Carcinogenesis

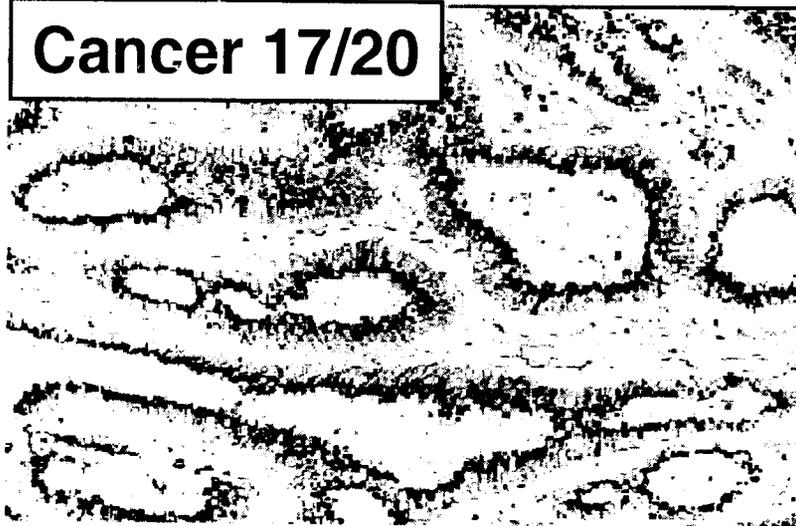
Normal 8/8



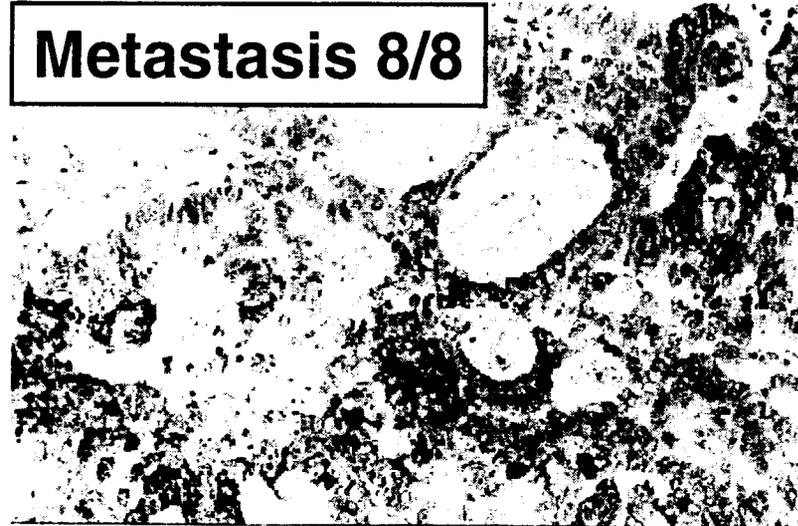
FAP 25/25



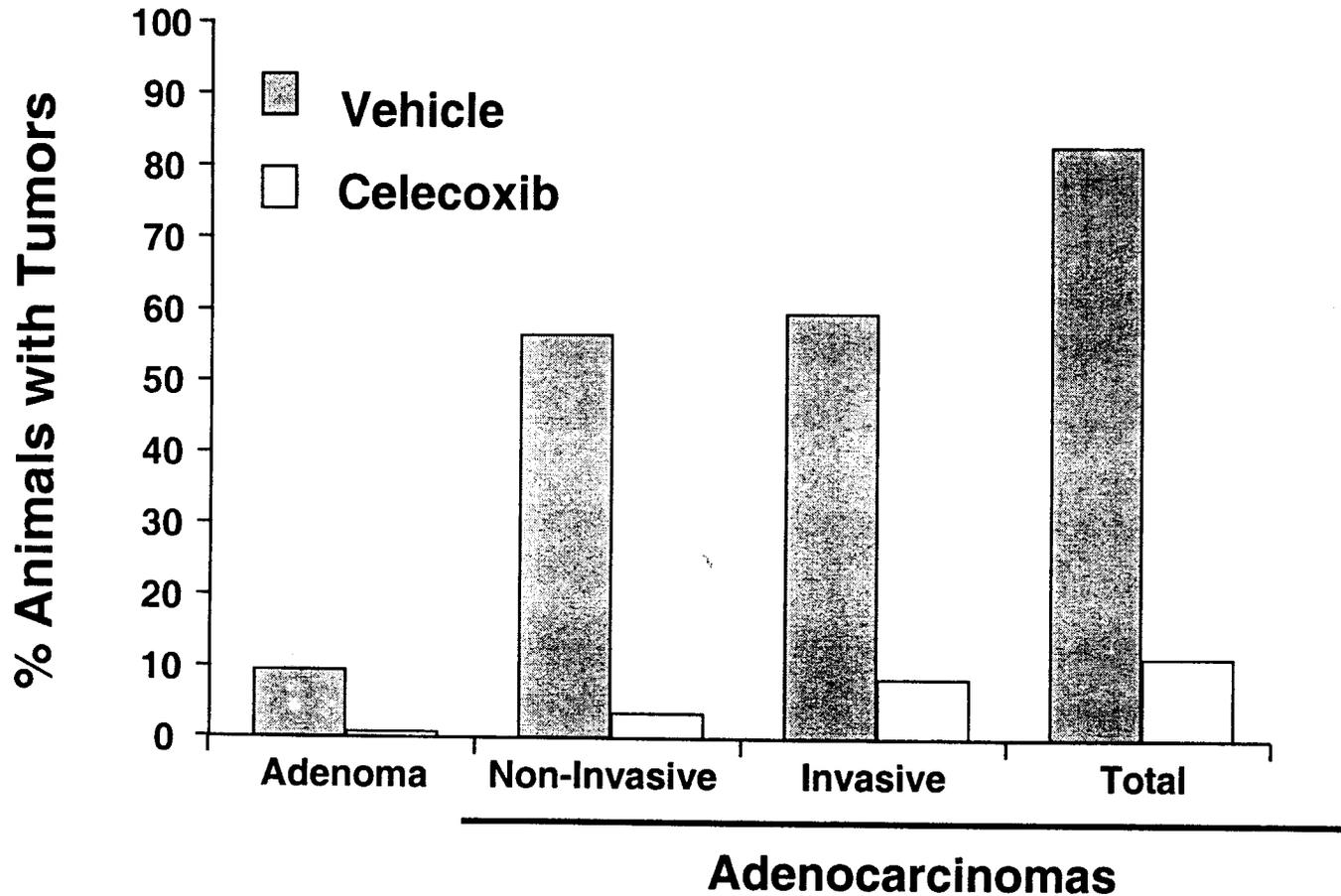
Cancer 17/20



Metastasis 8/8



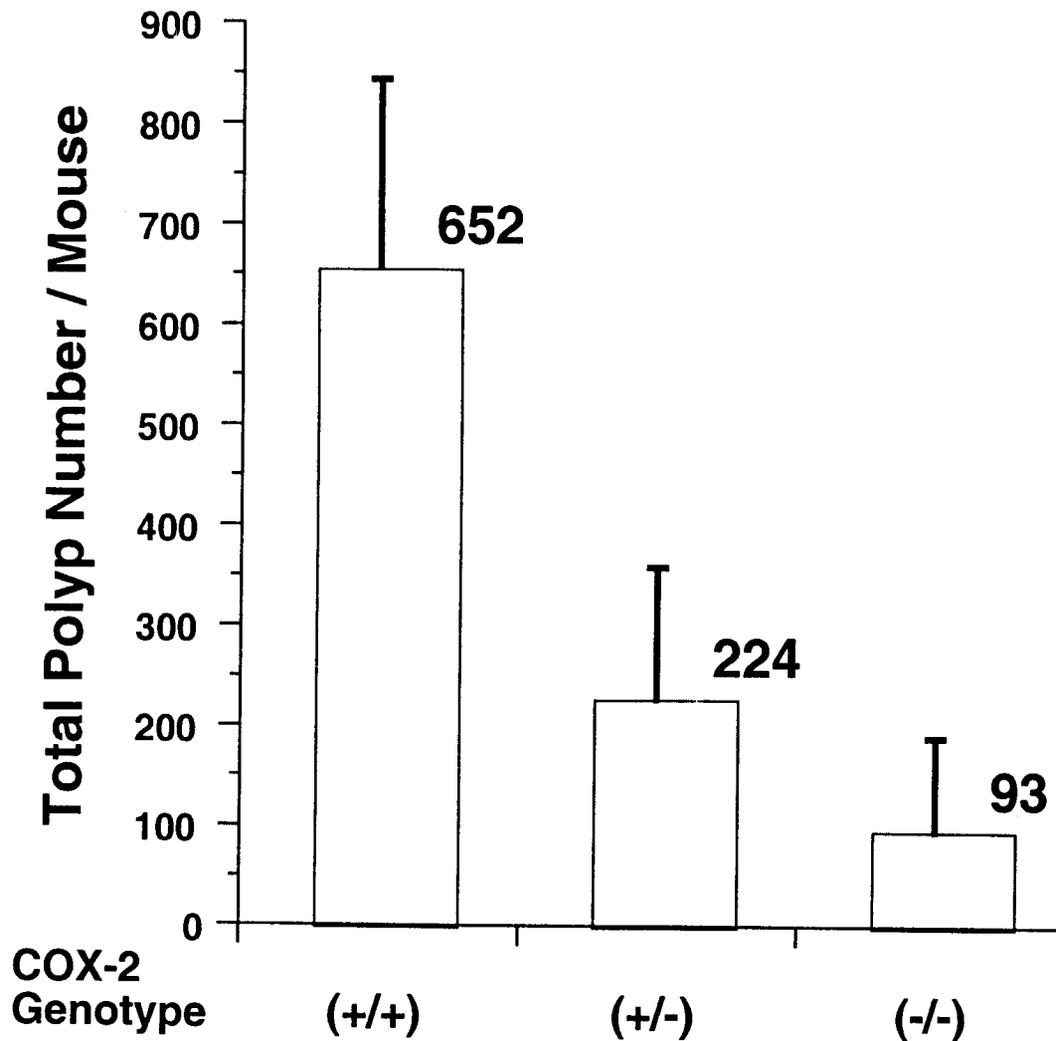
Celecoxib Decreases Colonic Tumor Incidence in the AOM Colon Cancer Model (52 Weeks)



n = 36 rats/group, 1500 mg/kg diet Celecoxib

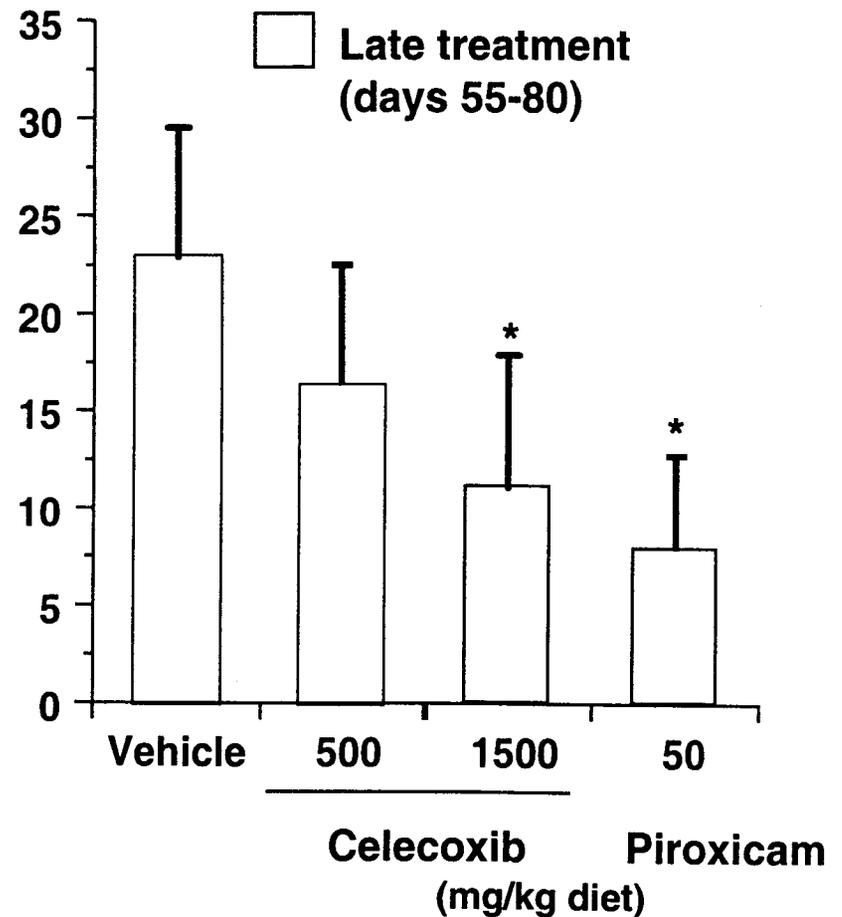
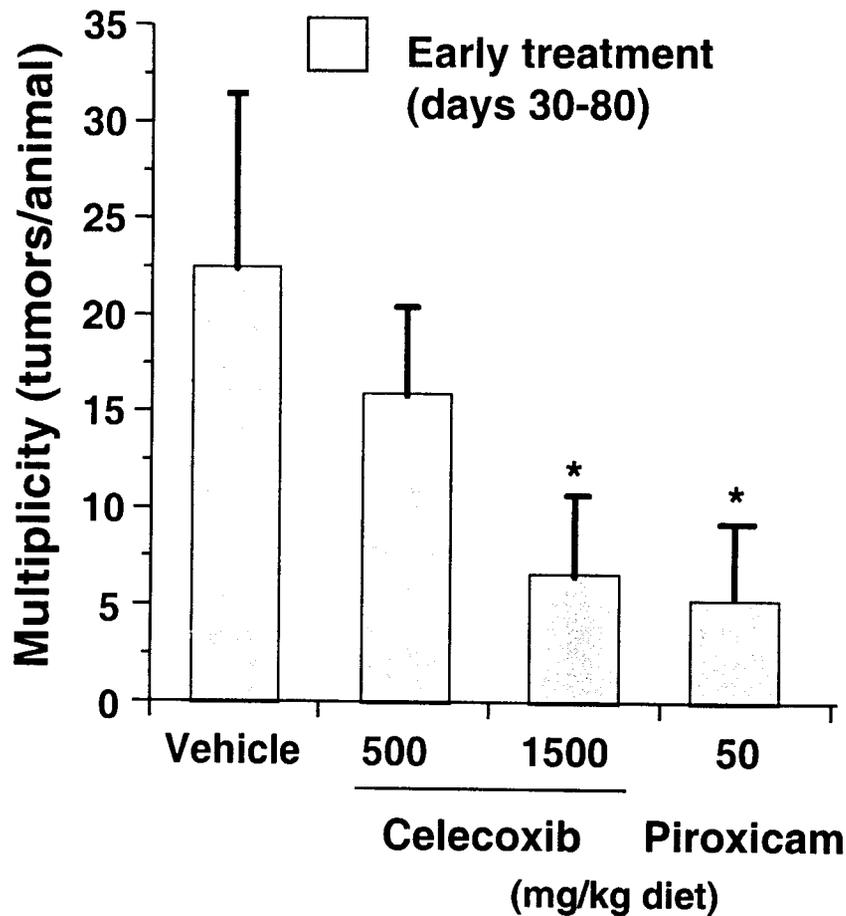
Kawamori *et al.* Cancer Research 58:409-412, 1998

COX-2 Gene Suppression Inhibits Intestinal Polyps in $Apc^{\Delta 716}$ Mice



Oshima *et al.* Cell 87:803, 1996

Celecoxib Inhibits Tumor Multiplicity in the MIN Mouse Model



* $P < 0.001$; $n=12$ /group

Jacoby *et al.* Proc Ann Meet Am Assoc Cancer Res, 1998

Summary

- **COX-2 is overexpressed in different stages of colon oncogenesis**
- **Genetic deletion of COX-2 inhibits polyp development**
- **Celecoxib reduces colon adenoma and cancer development with either early or late administration in the AOM and MIN models**
- **Celecoxib is effective and well-tolerated in animal models of cancer prevention**

Familial Adenomatous Polyposis Natural History, Management, and Opportunities for Improvement

Bernard Levin, M.D.

Vice President for Cancer Prevention

Division of Cancer Prevention

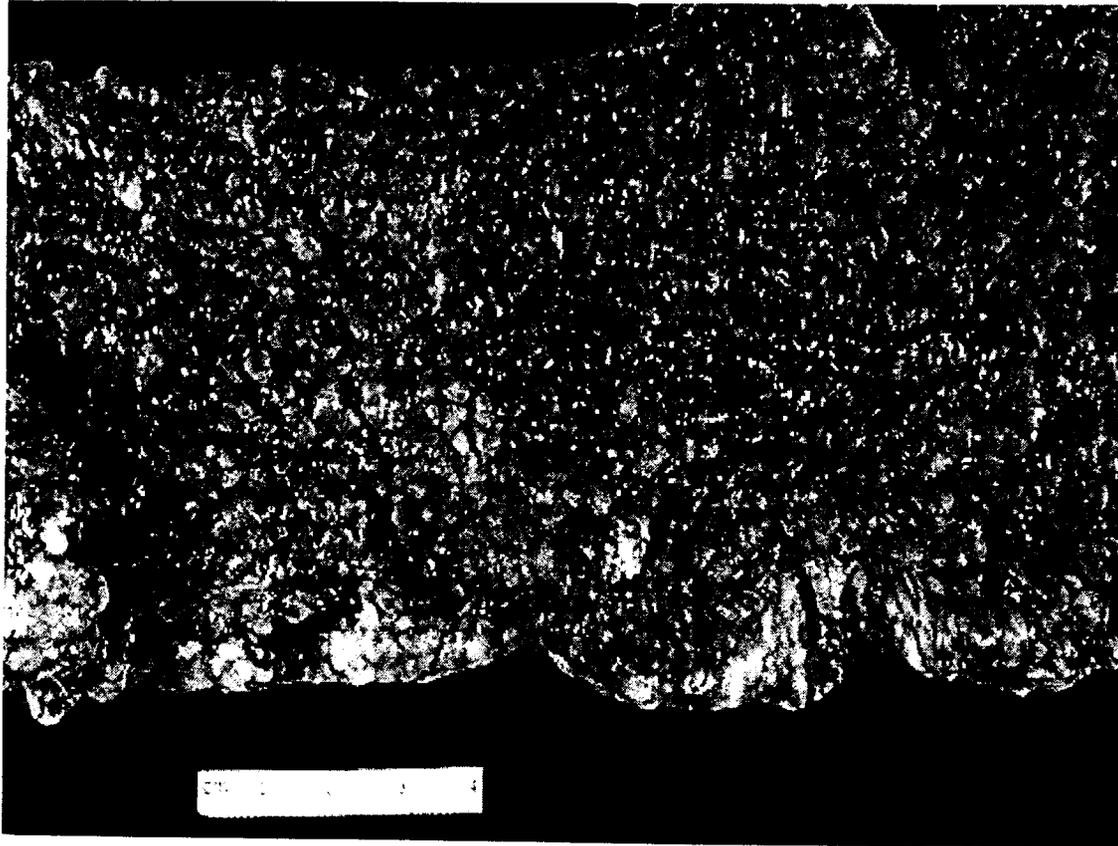
Professor of Medicine

U.T. M.D. Anderson Cancer Center

Familial Adenomatous Polyposis (FAP)

- **Uncommon, but devastating disease**
- **Autosomal-dominant inheritance**
 - **Germline APC mutations (5q21)**
 - **Clinical severity depends on genotype**
- **Affects 1 in 6850 to 1 in 31,250 individuals**
- **Provides insight into the biology of adenomas and colorectal cancer development**

Phenotype and Natural History of FAP



Colorectum - appearance of adenomatous polyps

- 15% by 10 years of age
- 50% by 15 years of age
- 75% by 20 years of age
- 90% by 30 years of age

Characteristics of Adenomatous Polyps

- **Polyps in FAP are adenomas and indistinguishable from sporadic adenomas**
- **Distribution of polyps in established FAP**
 - **Colorectum 100%**
 - **Duodenum up to 93%**

The Natural History of FAP

- **Symptoms**
 - Rectal bleeding, diarrhea/constipation, abdominal pain
- **At symptomatic diagnosis**
 - Average age = 36 years
 - 70% have a colorectal malignancy
- **Over lifetime**
 - 100% cancer risk...typically by 40-50 years
 - Average age at death = 42 years
- **Extracolonic manifestations**
 - Duodenal adenomas/dysplasia/cancer
 - Desmoid and other tumors

Screening and Surveillance

- **Flexible sigmoidoscopy for all 1st degree relatives**
- **Initial screening at 10 - 12 years of age**
- **Annual videorectoscopy until age 18 - 20**
- **Colonoscopy with dye spray at age 18 - 20 and every five years thereafter**
- **Initial upper endoscopy at age 20 - 25**
 - **Mild duodenal polyposis: monitor every 2 - 3 years**
 - **Significant duodenal polyposis: monitor every 6 - 12 months**
- ***Genetic counseling with genetic testing***

Colon Cancer in FAP

- **Untreated, mean age of diagnosis of colon cancer = 39 years**
- **87% develop cancer by age 45, 93% by age 50**
- **Life expectancy after diagnosis of cancer = 2.6 years**
- **Polyp number and age correlate with cancer risk**
 - **Each 10-year age group has 2.4-fold increase in risk**
- **Today, 25% of patients have cancer at diagnosis**

Current Surgical Management of FAP

- **Surgical prophylaxis - primary surgery**
 - **Colorectum**
 - **Colectomy with IRA (ileorectal anastomosis)**
 - **Proctocolectomy with IPAA (ileal-pouch-anal anastomosis)**
 - **Duodenum**
 - **No standard approach**
- **Additional (secondary) surgery when needed**

Need for Pharmacologic Agent in FAP

- **Despite standard screening, prophylactic colorectal surgery, and endoscopic surveillance,**
 - R.R. death = 3.35 (St. Mark's, 1993; n = 222)
 - **Causes of mortality**
 - Duodenal cancer
 - Desmoids
 - Rectal cancer
 - Perioperative complications/other extracolonic manifestations
- **Impact of surgery on quality of life**
 - Night time fecal incontinence
 - Sexual dysfunction
- **No approved pharmacologic agent**

Nugent, KP *et al.* Dis Colon Rectum, 1993

NSAID Evaluation in FAP

- **Database**
 - 100+ patients in uncontrolled studies
 - 3 controlled trials (N = 24 in largest study)
- **Findings**
 - Reduction and regression of polyps observed
 - No consistent effect on duodenal neoplasia
 - Studies not comparable to each other due to method differences
- **Concern**
 - NSAID side-effects

Possible Clinical Benefits of Celecoxib in FAP Management

- **Reduction and regression of polyps facilitates endoscopic surveillance**
- **Delay or prevent secondary FAP related GI surgery**
- **Reduce or delay duodenal neoplasia**
- **Delay or prevent emergence of disease in adolescents**
- **Favorable safety profile for long-term administration**

Celecoxib in Familial Adenomatous Polyposis (FAP)

Clinical Study and Efficacy

**Ernest T. Hawk, M.D., M.P.H.
Chief, GI Cancer Research Group
NCI-Division of Cancer Prevention**

Efficacy Presentation Outline

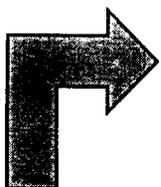
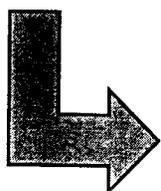
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- **Trial Design**
- **Methods**
- **Results**
 - **Demographics**
 - **Colorectal**
 - **Duodenal**
- **Conclusion**

FAP PATHOPHYSIOLOGY

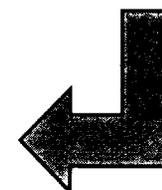
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NSAID CANCER PREVENTION

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NCI-CONTRACTED TRIAL OF CELECOXIB IN FAP



G. D. SEARLE

- COX-2 technology
- Celecoxib safety database
- Celecoxib preclinical data

FAP PATIENTS

- Unmet clinical need
- Limited cohort
- MDACC & St. Mark's registries

Efficacy Presentation Outline

- **Background**
- **Trial Design**
- **Methods**
- **Results**
 - **Demographics**
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 - **Duodenal**
- **Conclusion**

Trial Design

Description:	Double-blind, placebo-controlled study of celecoxib in persons with Familial Adenomatous Polyposis (FAP)
Treatment Groups:	Placebo Celecoxib (100, 400 mg po BID)
Subjects:	N = 81 (17:32:32) planned 2 replacement patients enrolled in 100 mg BID group
Duration of Therapy:	6 months
Sites:	U.T. M.D. Anderson, St. Mark's

Study Design Considerations

- **Dose Selection**
 - **100 & 400 mg BID doses selected**
 - **Preclinical data**
 - **Phase II OA/RA efficacy and safety data**
- **Study Duration**
 - **Previous NSAID studies in FAP**

Eligibility Criteria

- **Inclusion Criteria**
 - **Diagnosis of FAP**
 - **Retained colorectal segment**
 - **5 polyps \geq 2mm in focal colorectal segment**
 - **Abstinent from frequent NSAID use > 6 months**
- **Exclusion Criteria**
 - **Gastric ulcers or erosions**
 - **Expected colectomy within 8 months**
 - **Previous colectomy within prior 12 months**
 - **Metastatic cancer**

Study Endpoints

- **Primary Efficacy**
 - Percent change in the number of colorectal adenomas ($\geq 2\text{mm}$) at 6 months
- **Secondary Efficacy**
 - Percent change in the area of duodenal polyposis at 6 months
- **Safety and Tolerability**

Supporting Analyses

- **Number/percent of responders**
- **Residual polyp size**
- **Polyp burden (sum of polyp diameters)**
- **Endoscopy videotape review**
 - **Colorectum**
 - **Duodenum**

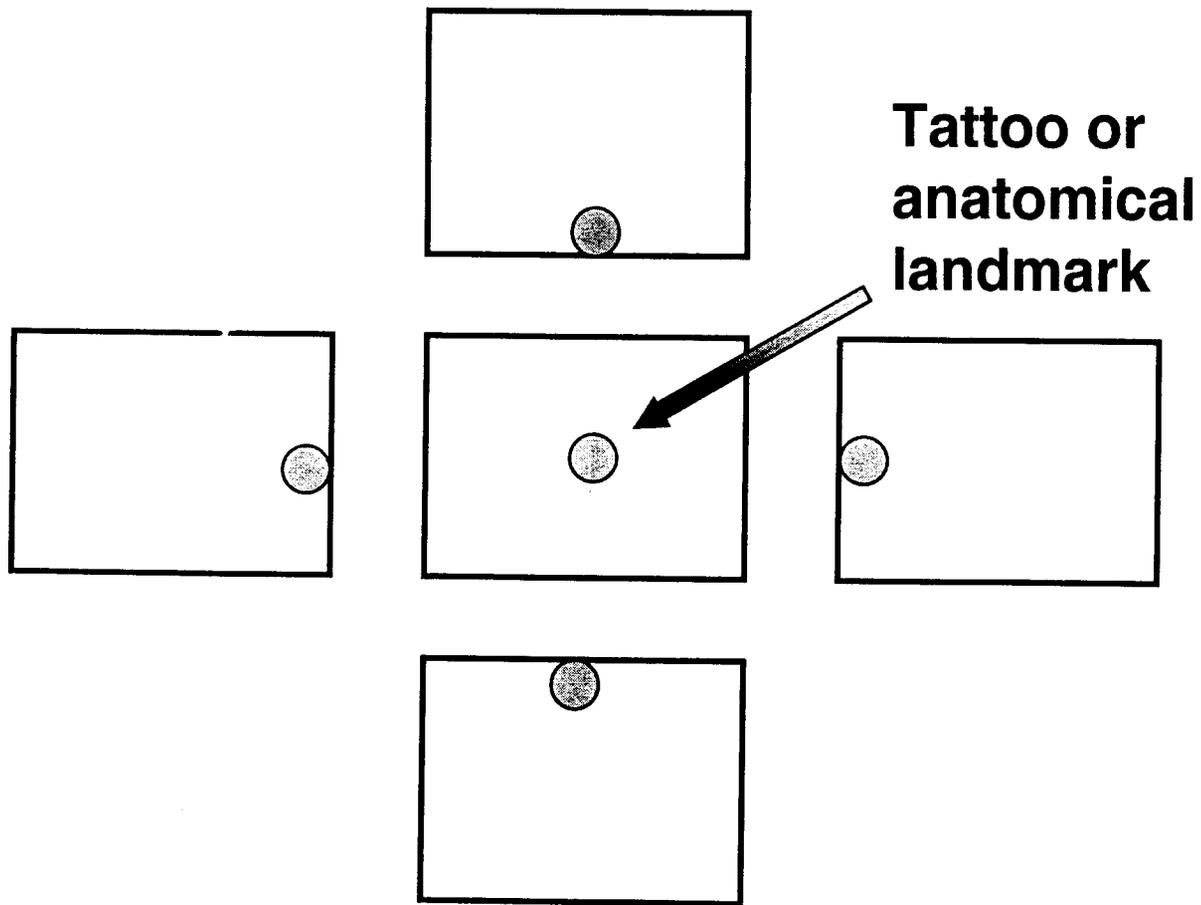
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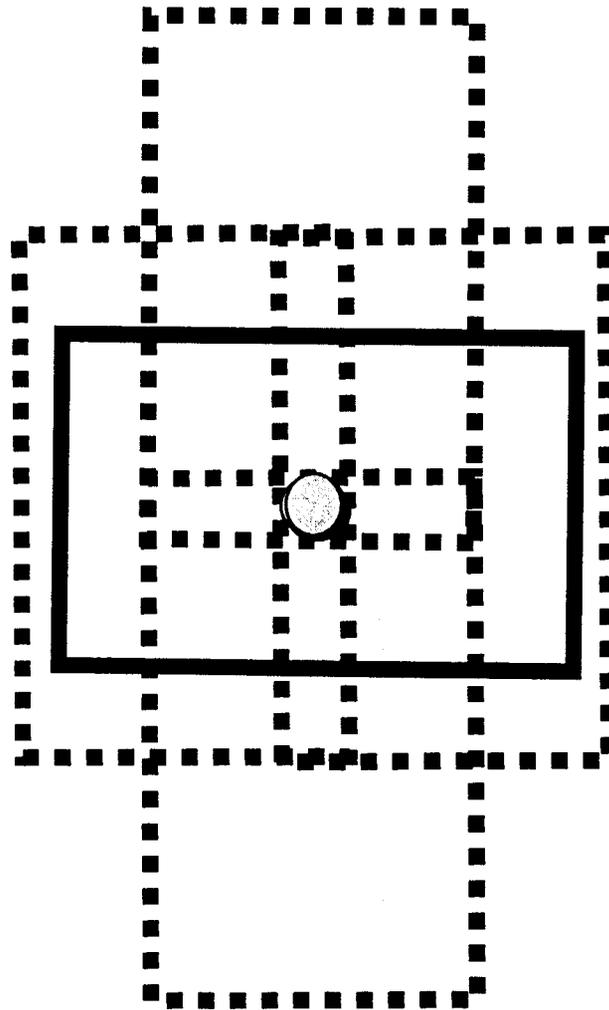
Methods - Source Documentation

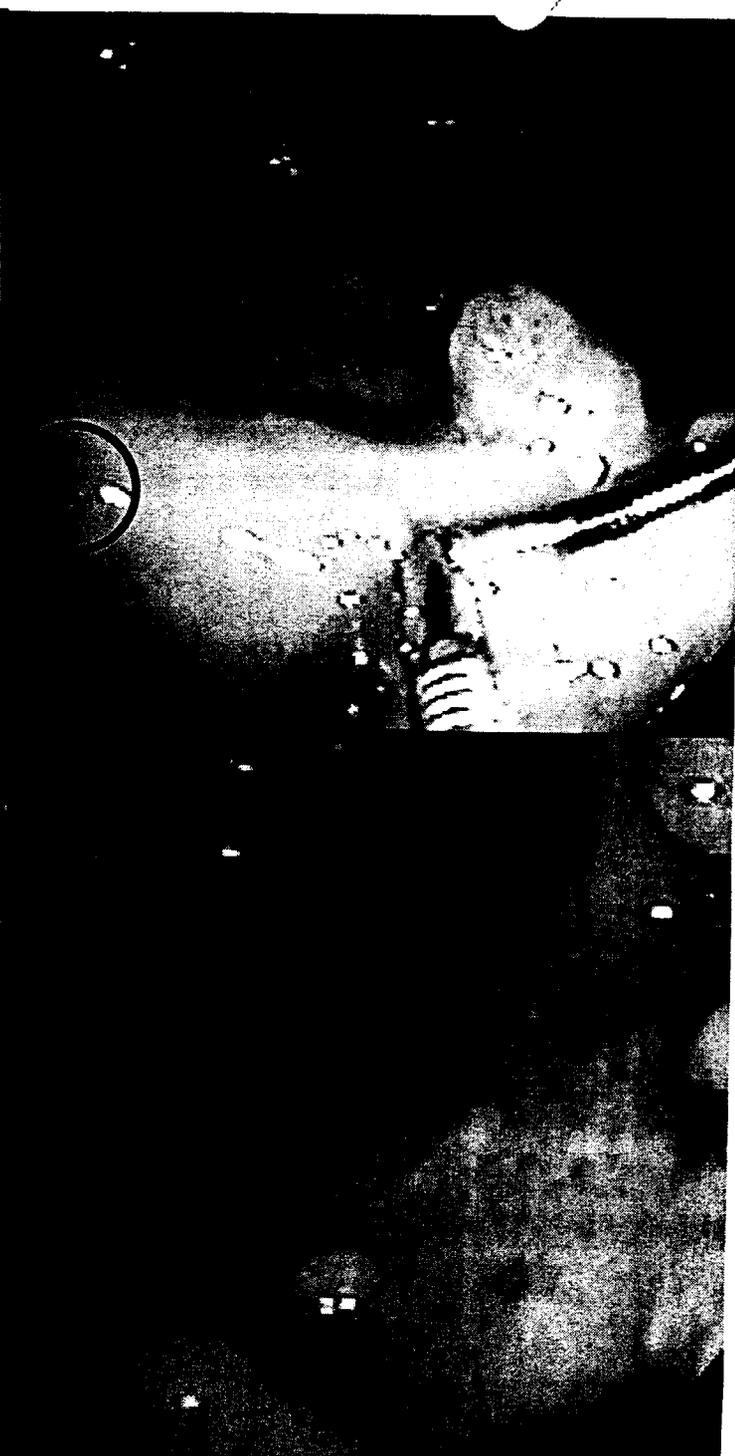
- **Focal Assessments**
 - **Photographs of GI tract segments designated by anatomical markings or tattoos**
- **Global Assessments**
 - **Expert reviews of colorectal and duodenal endoscopic videotapes**

Still Color Photography



Orientation of Photographs

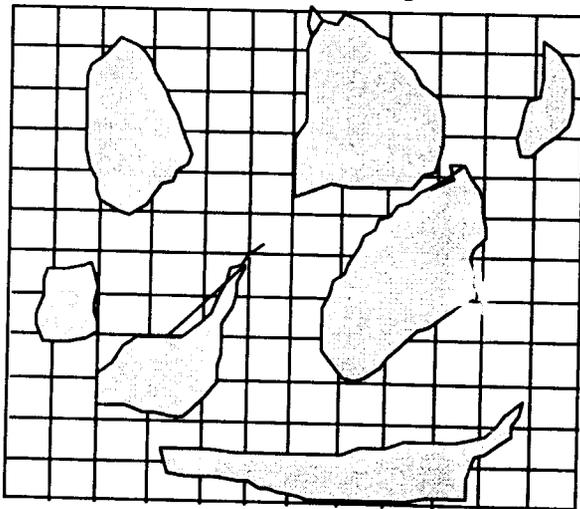




Measurement of Duodenal Disease

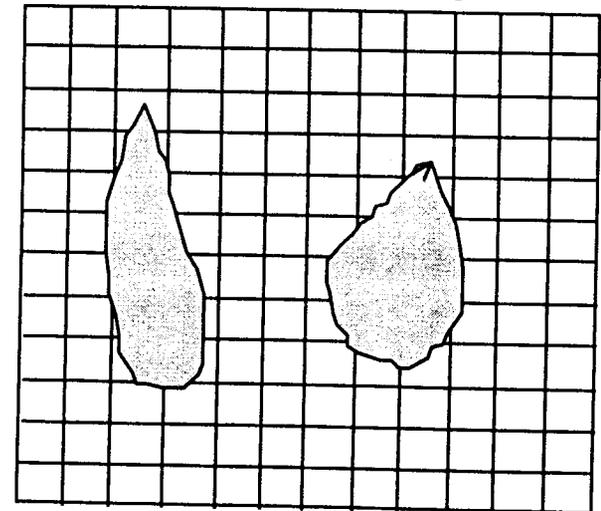
- Based on discrete photographs

High Density



Approximate Area Covered: 47%

Low Density



Approximate Area Covered: 16%

Average percent area covered with plaque-like polyps reported

$$0.47 + 0.16 = .63$$

$$0.63/2 = 31.5\% \text{ covered}$$

Duodenum Photos



High Density



Low Density

Methods - Video Review Sessions

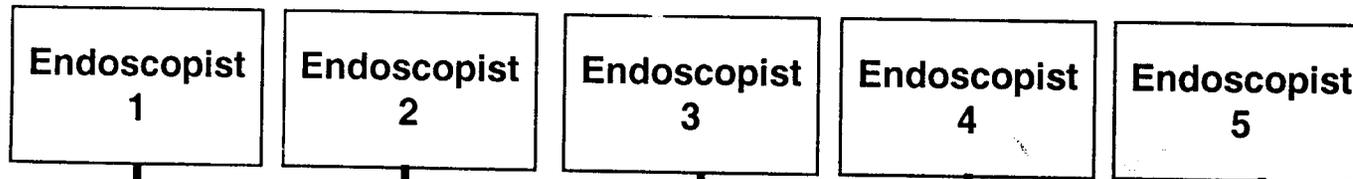
- **Endoscopy videotape reviewed blinded by five experienced endoscopists**
 - **2 from U.T. M.D. Anderson**
 - **2 from St. Mark's Hospital**
 - **1 from Roswell Park, a non-participating polyposis center**

Methods - Video Review Sessions



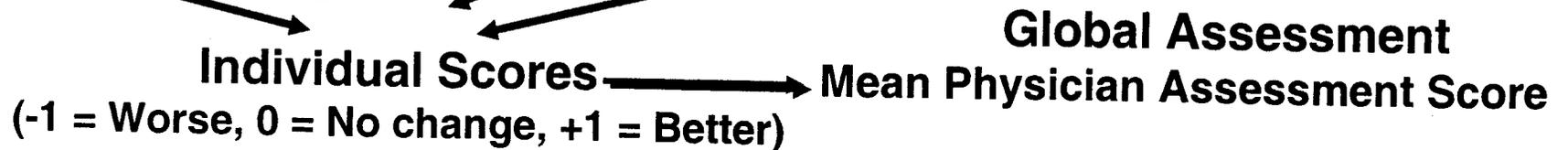
Endoscopy Videotape Blinded Review

- Treatment Group
- Pre/post sequence
- Patient identification



Review Panel

- 5 Endoscopists
- Independent assessment



Efficacy Presentation Outline

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Baseline Demographics

	Celecoxib			P-value*
	Placebo (N=17)	100 mg BID (N=34)	400 mg BID (N=32)	
Age (years)				0.013
Mean	41.2	39.5	33.0	
Range	20-64	19-56	20-60	
Race/Ethnic Origin				0.819
Black	1	1	1	
Caucasian	16	31	28	
Hispanic/Latin American	0	2	3	
Gender				1.000
Female	7	15	14	
Male	10	19	18	
Mean Focal Polyp Number	15.5	11.5	12.3	0.66
Mean Polyp Size (mm)	2.9	2.9	2.9	0.64

* Kruskal-Wallis (continuous) or Fisher's Exact (categorical)

Patient Enrollment by Center

	Placebo	Celecoxib 100 mg BID	Celecoxib 400 mg BID
US, U.T. M.D. ANDERSON (N=42)	9	17	16
UK, St. MARK'S (N=41)	8	17	16
TOTAL	17	34	32

Baseline Surgical Status of the Colon

	Placebo	Celecoxib 100 mg BID	Celecoxib 400 mg BID	p-value
Intact Colon (%)	5 (29.4)	8 (23.5)	12 (37.5)	
Colectomy (%)†	10 (58.8)	25 (73.5)	18 (56.3)	
Proctocolectomy (%)††	2 (11.8)	1 (2.9)	2 (6.3)	
Total	17 (100)	34 (100)	32 (100)	0.494*

† Colectomy - Includes 6 patients with portion of sigmoid remaining

†† Proctocolectomy - Includes one patient with ileostomy

* Pearson's Chi-square test

Patients Evaluated for Focal Assessments

Intent to Treat

- **Total Number Enrolled**
 - 83 patients
- **Colorectal Endpoint**
 - 77 colorectal patients
- **Duodenal Endpoint**
 - 6 with only duodenal plaque-like disease
 - 46 of the colorectal patients who also had duodenal plaque-like disease

Patients Evaluated for Global Assessments

Intent to Treat

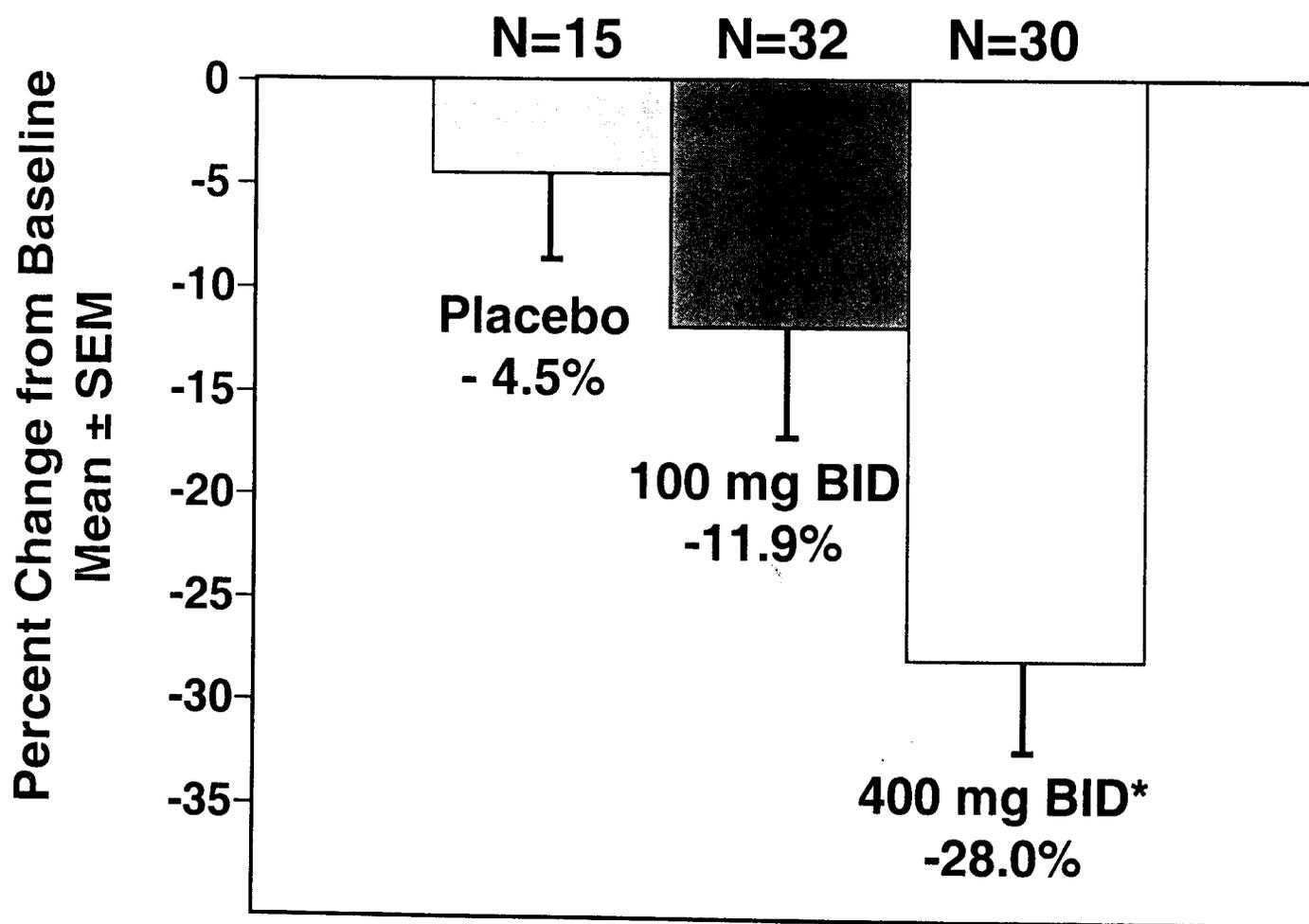
- **Total Number Enrolled**
 - 83 patients
- **Colorectal Endpoint**
 - 73 colorectal patients
- **Duodenal Endpoint †**
 - 78 patients

† Assessment of mucosal appearance, including plaque-like disease

Efficacy Presentation Outline

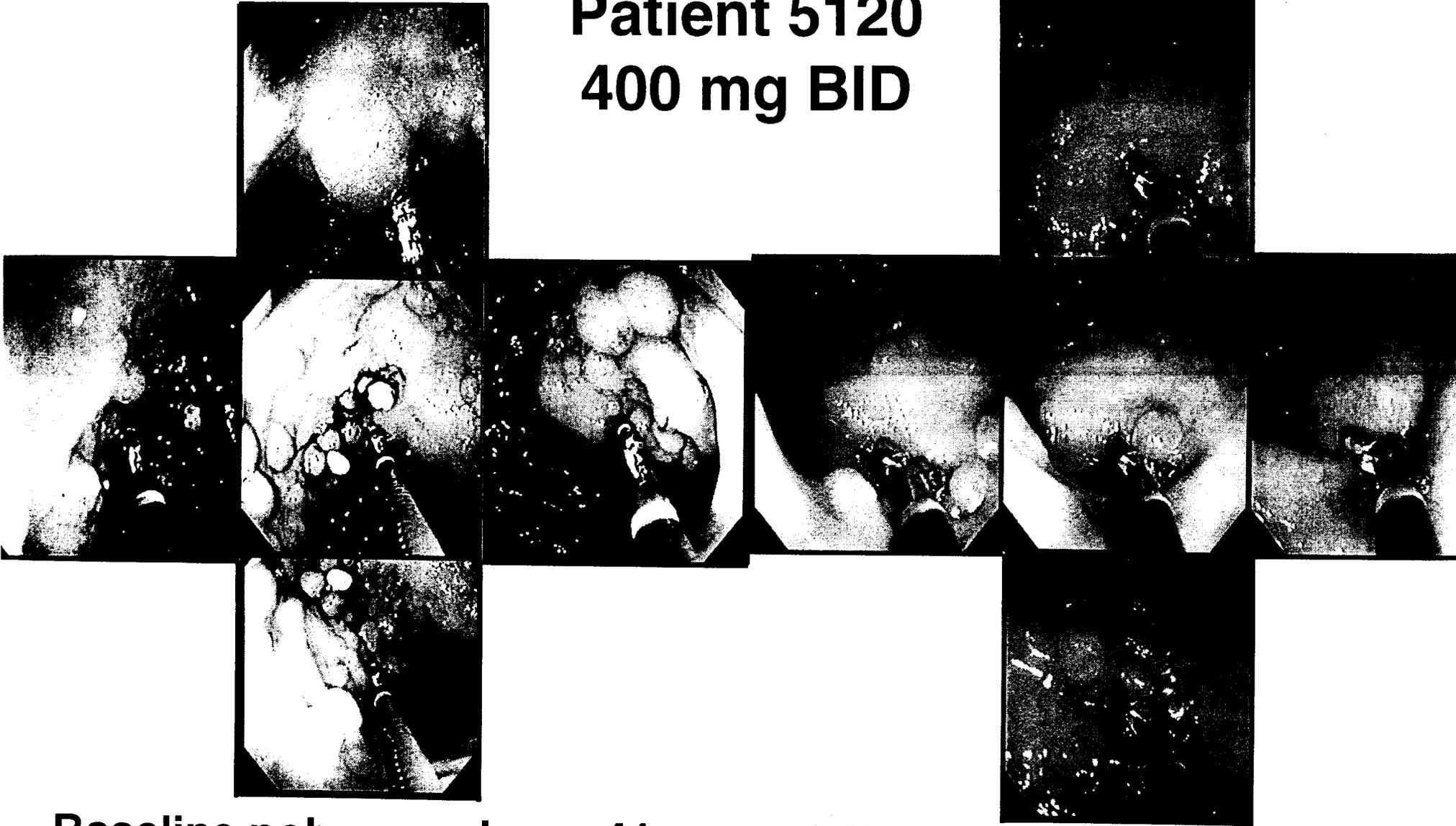
- **Background**
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Percent Change in the Number of Colorectal Polyps



* P = 0.003 versus placebo (Wilcoxon rank sum)

Patient 5120
400 mg BID

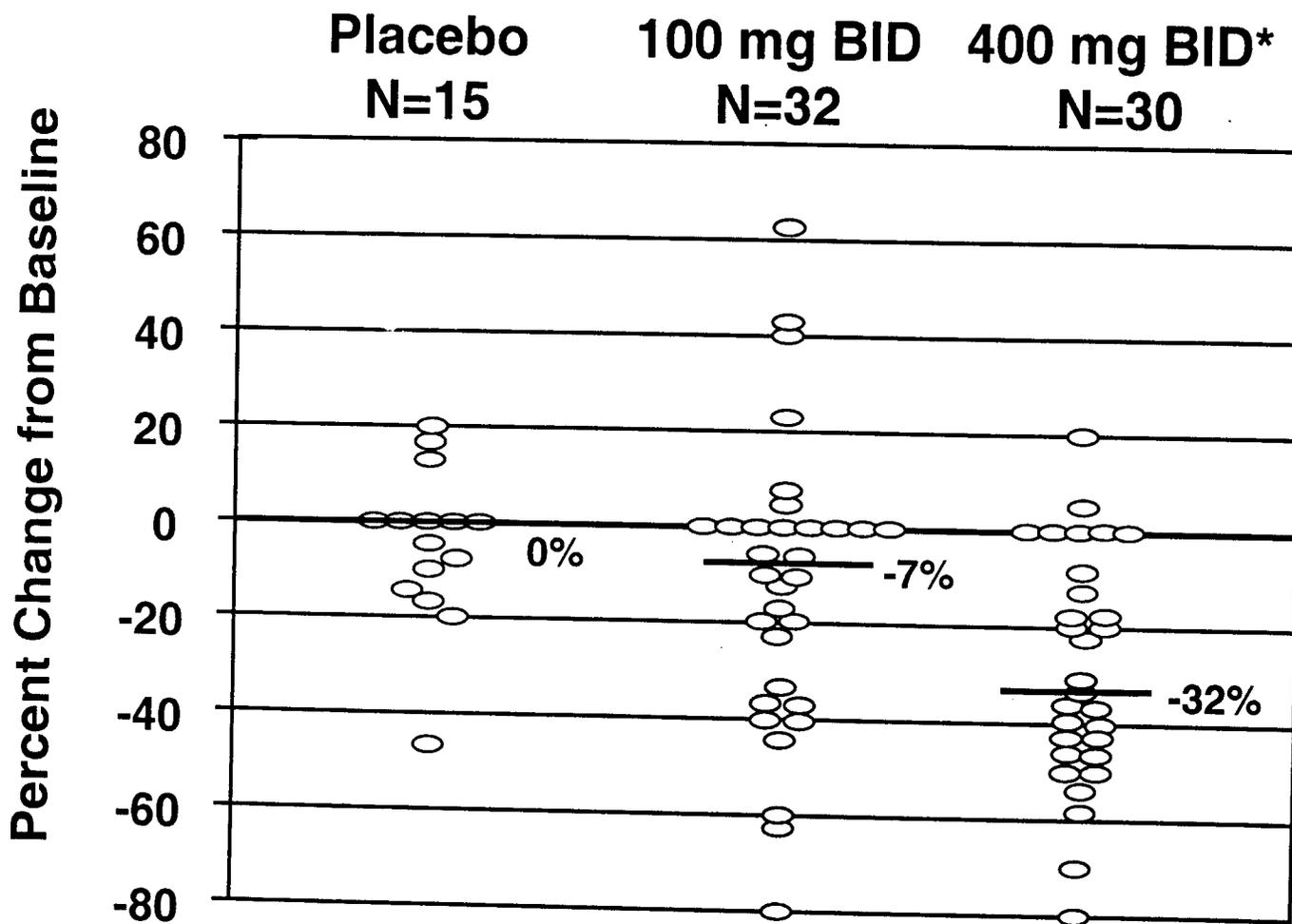


Baseline polyp number = 41

6 Month polyp number = 21

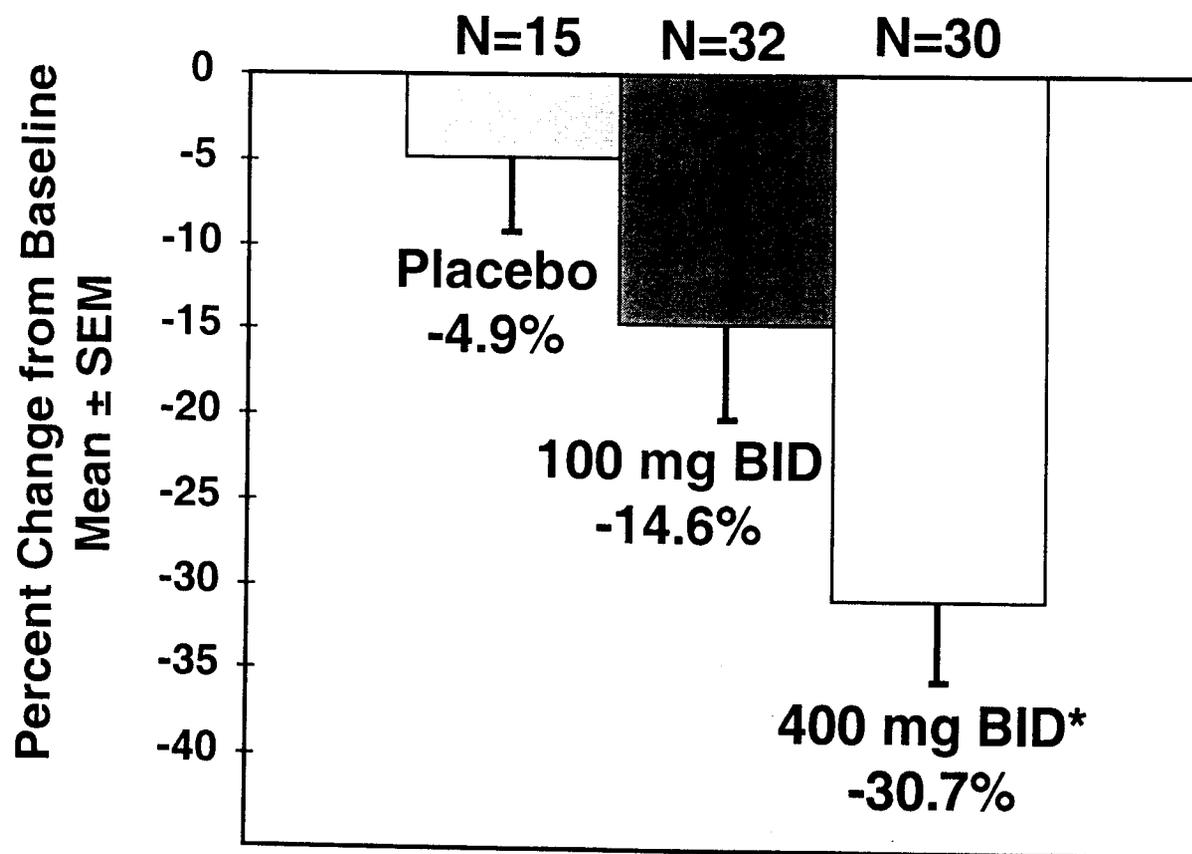
Percent change = - 48.8%

Percent Change in Number of Colorectal Polyps (Individual Patients; Median Results)



* P = 0.003 versus placebo

Percent Change in Colorectal Polyp Burden (Sum of Polyp Diameters)



* P = 0.001 versus placebo

Focal Assessments - Colorectum

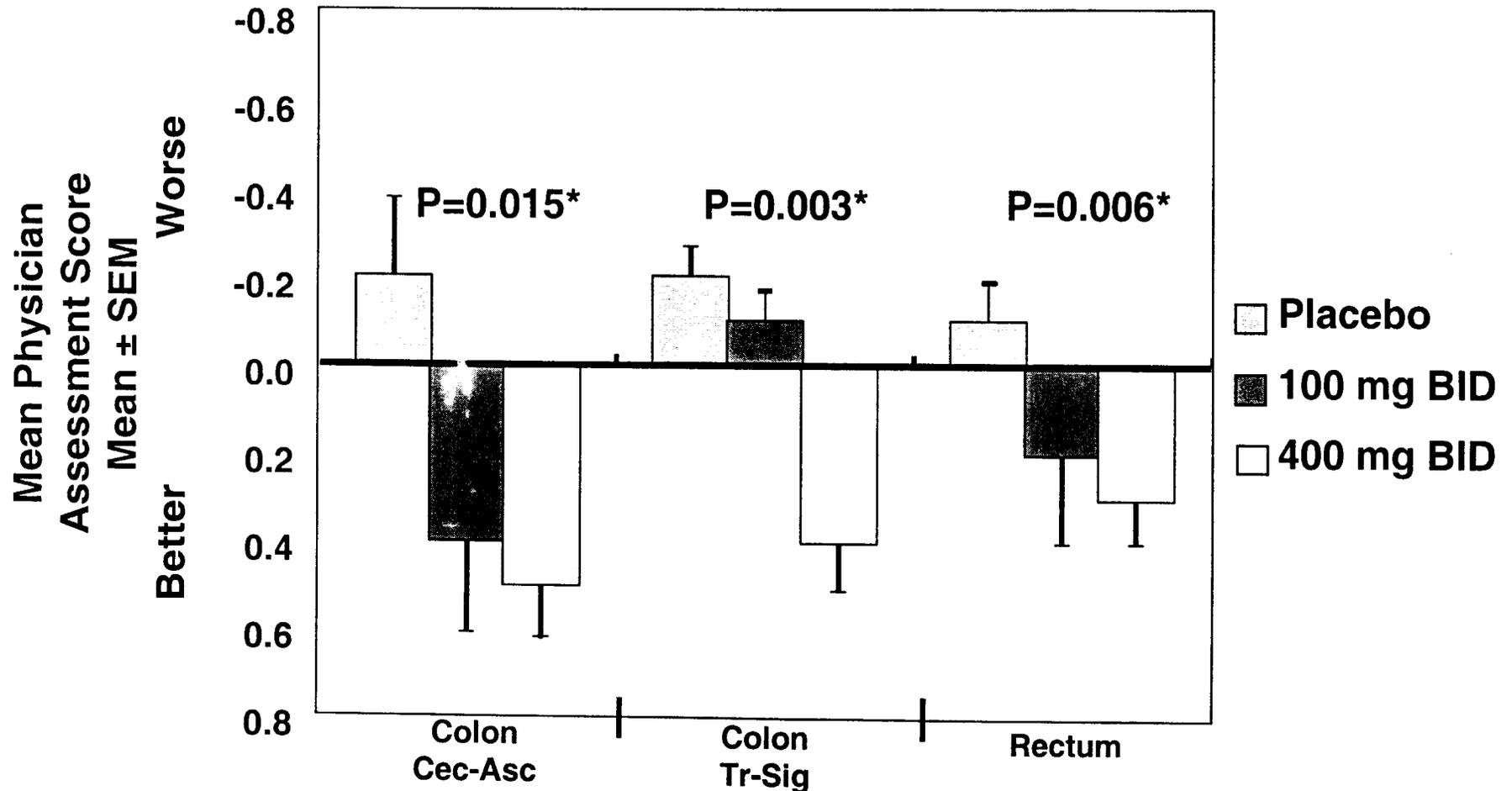
Primary and Supportive Analyses

	Placebo N=15	Celecoxib	
		100 mg BID N=32	400 mg BID N=30
Number of Polyps	-4.5%	-11.9%	-28.0%*
% Responders (≥ 25% reduction)	6.7%	31.2%	53.3%*
Residual Polyp Size (mm)	-0.7%	-3.0%	-4.9%
Polyp Burden	-4.9%	-14.6%	-30.7%*

* P ≤ 0.003 versus placebo

Global Assessment - Colorectum

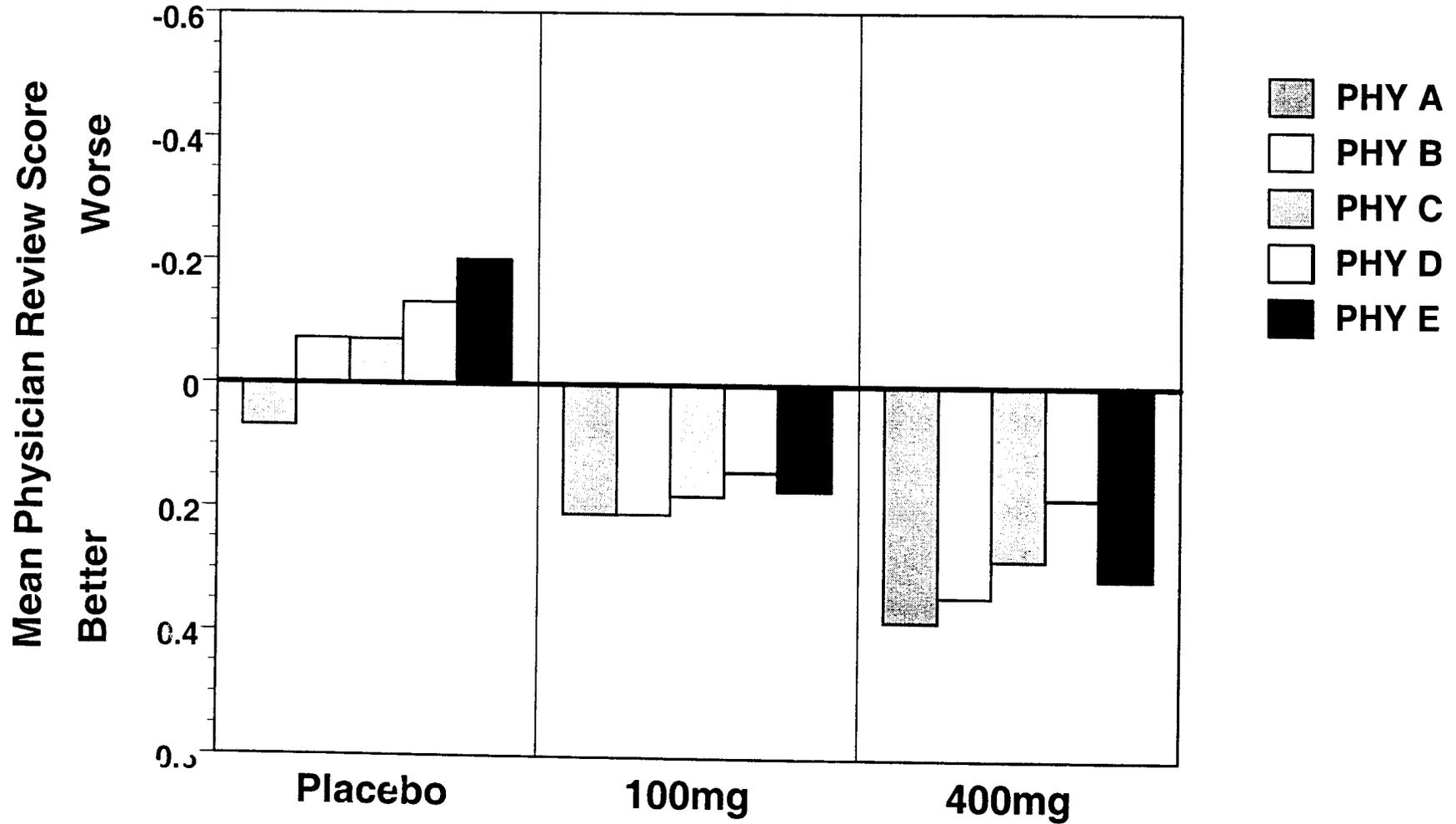
Videotape Scoring by Anatomic Segment



Assessment Scale: -1 = Worse, 0 = No Change, +1 = Better

* 400 mg BID versus placebo

Individual Reviewer Video Assessment of the Rectum



Summary: Celecoxib Efficacy in Colorectum

- **Focal Assessment**
 - Polyp number reduced
- **Supporting Focal Assessment Analyses**
 - More responders in 400 mg BID group
 - Polyp burden reduced
- **Global Assessment**
 - Improvement across all regions of colorectum

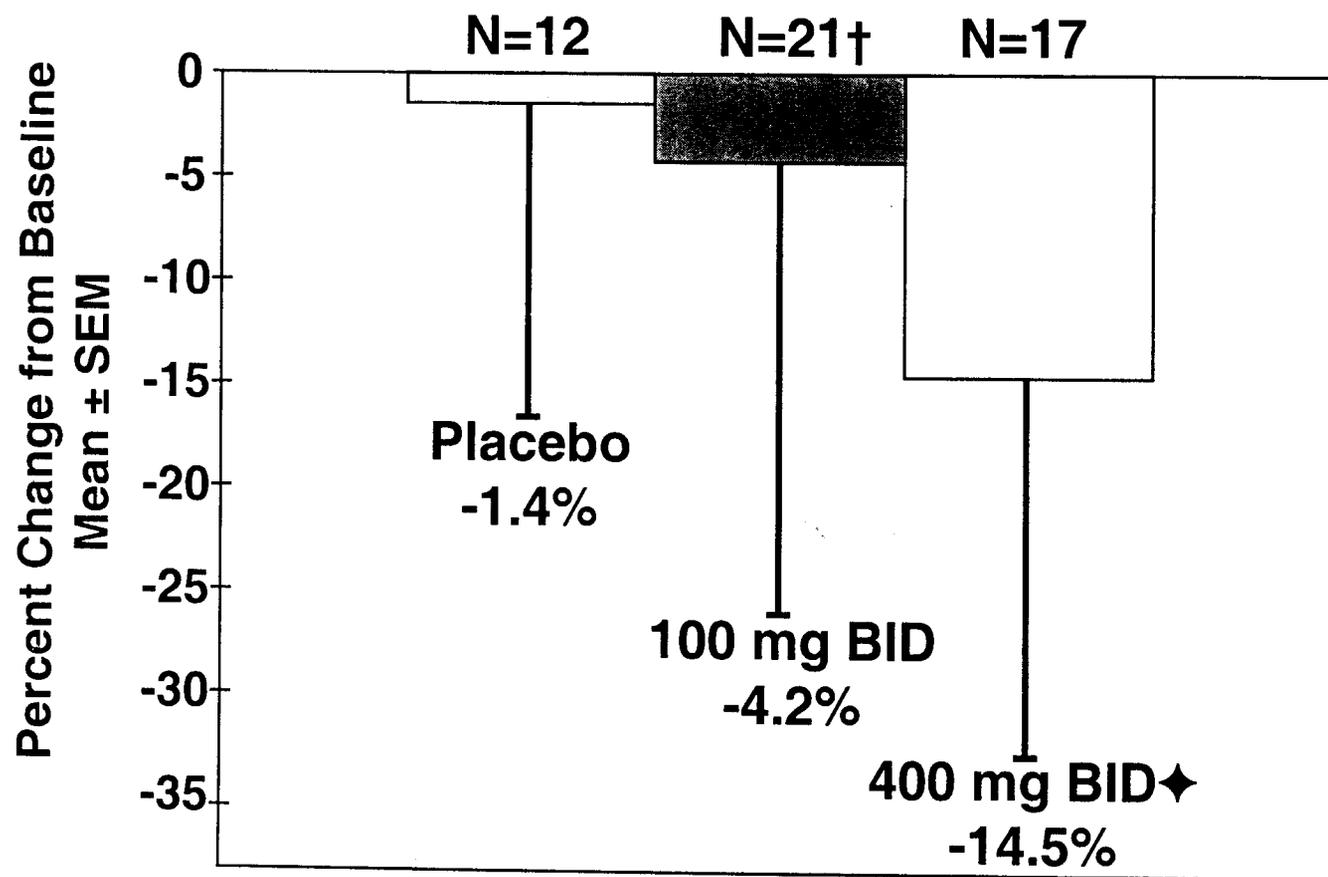
Conclusion: Celecoxib Efficacy in Colorectum

- **All analyses confirm a consistent, substantial, and statistically significant improvement in colorectal polyposis in the 400mg BID group**

Efficacy Presentation Outline

- **Background**
- **Trial Design**
- **Methods**
- **Results**
 - **Demographics**
 - **Colorectal**
 - **Duodenal**
- **Conclusion**

Percent Change in Area of Duodenal Plaque-Like Polyps



† Two patients with no baseline disease excluded

◆ P = 0.436 versus placebo (Wilcoxon rank sum)

Patient 5120
400mg BID

Duodenum Photos

Percent change = - 100%



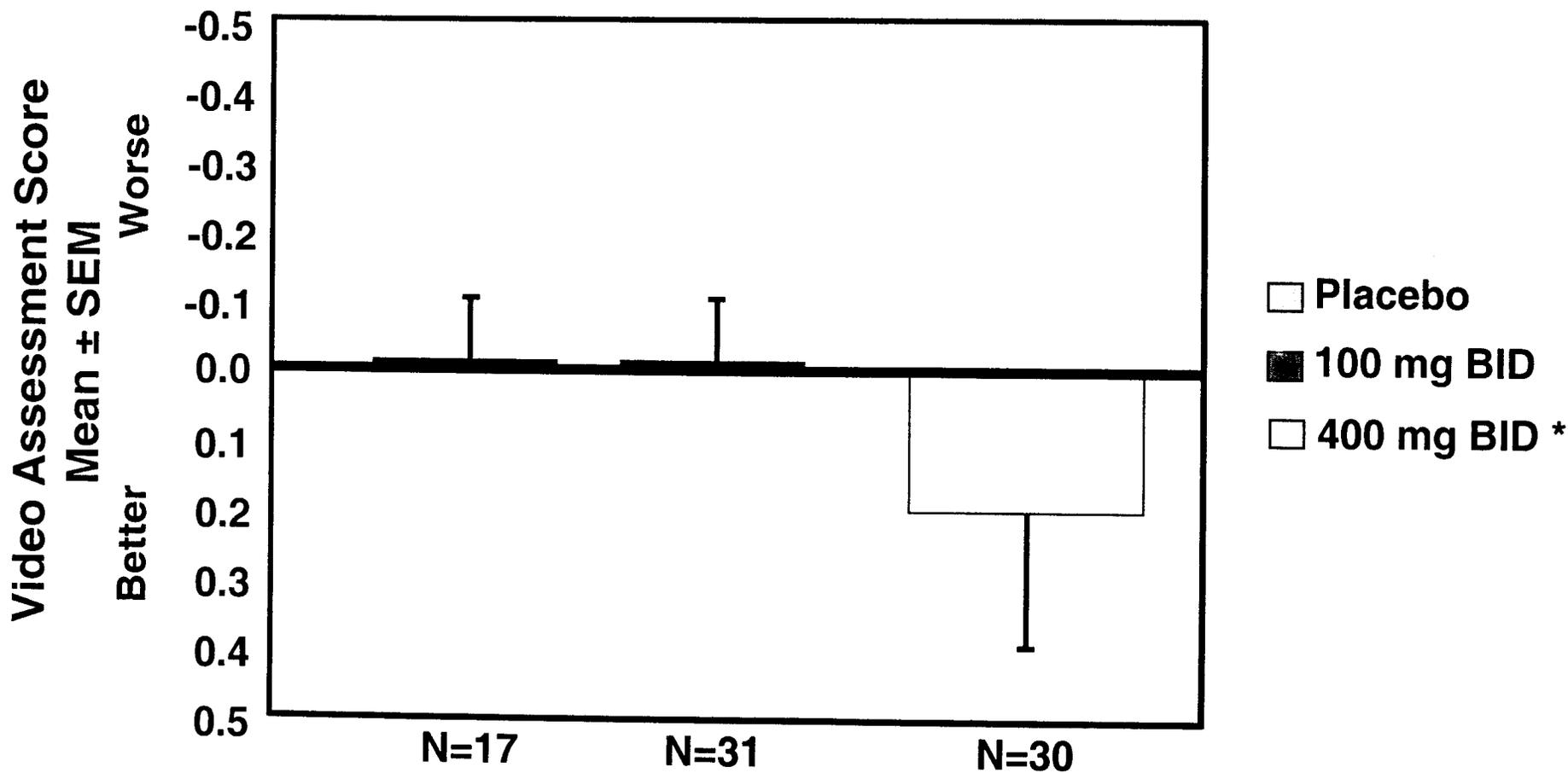
Baseline



6 Month

Global Assessment - Duodenum

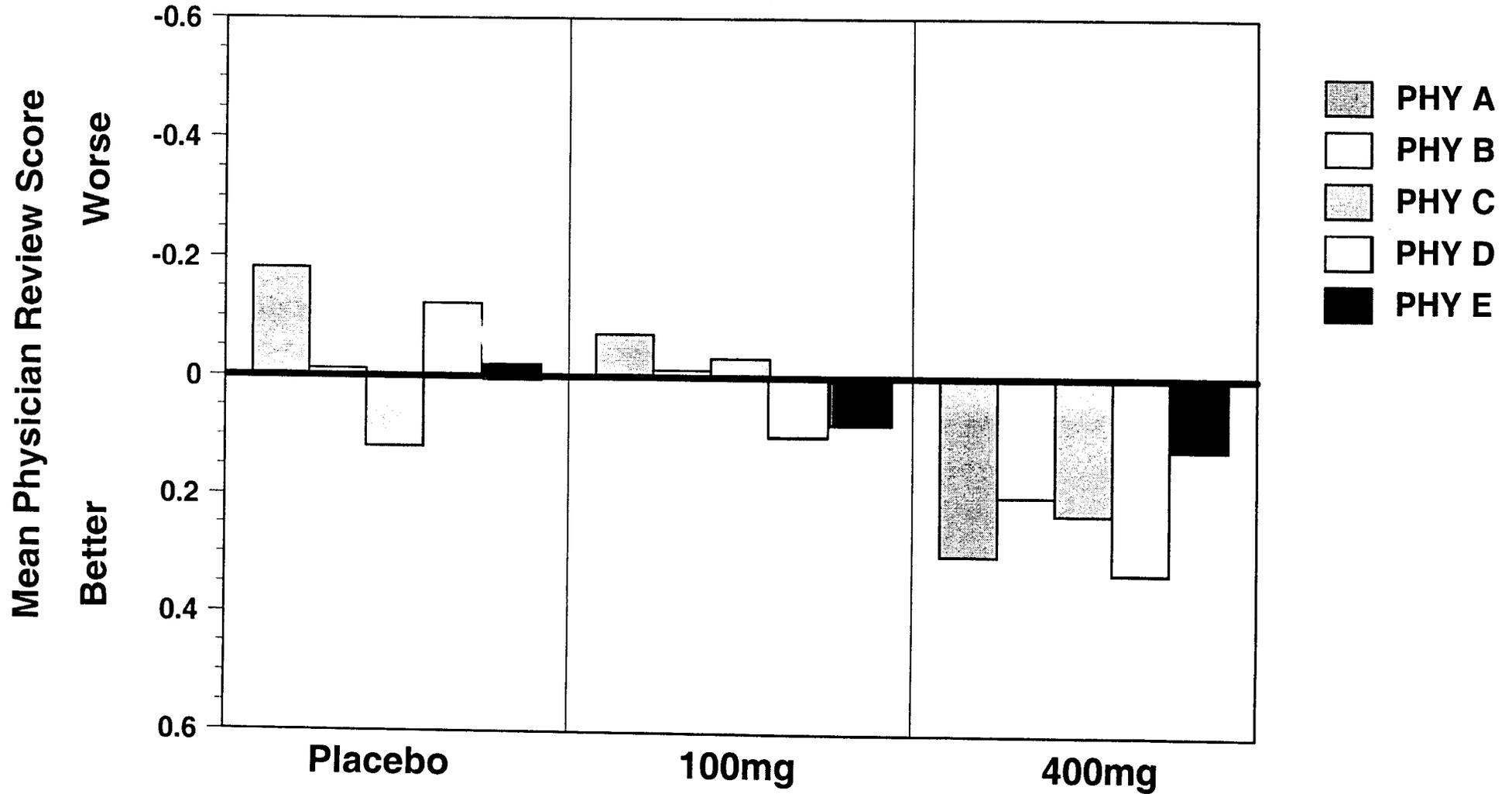
Videotape Scoring by Expert Panel



Assessment Scale: -1 = Worse, 0 = No Change, +1 = Better

* P = 0.033 versus placebo (Wilcoxon rank sum)

Individual Reviewer Video Assessment of the Duodenum



Summary: Celecoxib Efficacy in Duodenum

- **Focal Assessment**
 - Trend for response in 400 mg BID group (NS)
- **Global Assessment**
 - Significant improvement by video endoscopy in 400 mg BID group
- **Conclusion**
 - Findings suggestive of a beneficial effect

Efficacy Presentation Outline

- **Background**
- **Trial Design**
- **Methods**
- **Results**
 - **Demographics**
 - **Colorectal**
 - **Duodenal**
- **Conclusion**

Overall Celecoxib Efficacy Conclusions

- **Celecoxib 400 mg BID results in:**
 - **Focal**
 - **Reduction and regression of colorectal polyposis**
 - **Global**
 - **Improvement in endoscopic appearance of colorectum and duodenum**

Clinical Study Safety and Follow-Up Plan

Gary B. Gordon, M.D., Ph.D.
Director, Cancer Prevention/Treatment
Clinical Research
Searle

Safety Presentation Outline

- **Background**
- **Methods**
- **Patient Disposition**
- **Adverse Events**
- **Conclusion**

General Clinical Safety of Celecoxib in OA/RA

- **Well tolerated in over 9,400 patients (NDA)**
- **Over 1 million patient years of exposure in post marketing experience**
- **Low incidence of adverse events**
- **Similar short and long term safety profiles**
- **No dose-related increase in adverse events**

North American Arthritis Trials

Adverse Events with $\geq 5\%$ Incidence in Any Treatment

<u>Adverse Event</u>	<u>Placebo (n=1864)</u>	<u>Celecoxib† (n=4146)</u>	<u>Celecoxib 400 mg BID (n=615)</u>	<u>NSAID (n=2098)</u>
Headache	20.2	15.8*	14.5*	14.8*
Dyspepsia	6.2	8.8*	8.1*	12.0* **
URTI	6.7	8.1*	7.0	9.9
Diarrhea	3.8	5.6*	6.5*	6.1
Sinusitis	4.3	5.0	5.4	4.6
Abdominal Pain	2.8	4.1	3.3	8.2* **
Nausea	4.2	3.5	3.6	5.6* **

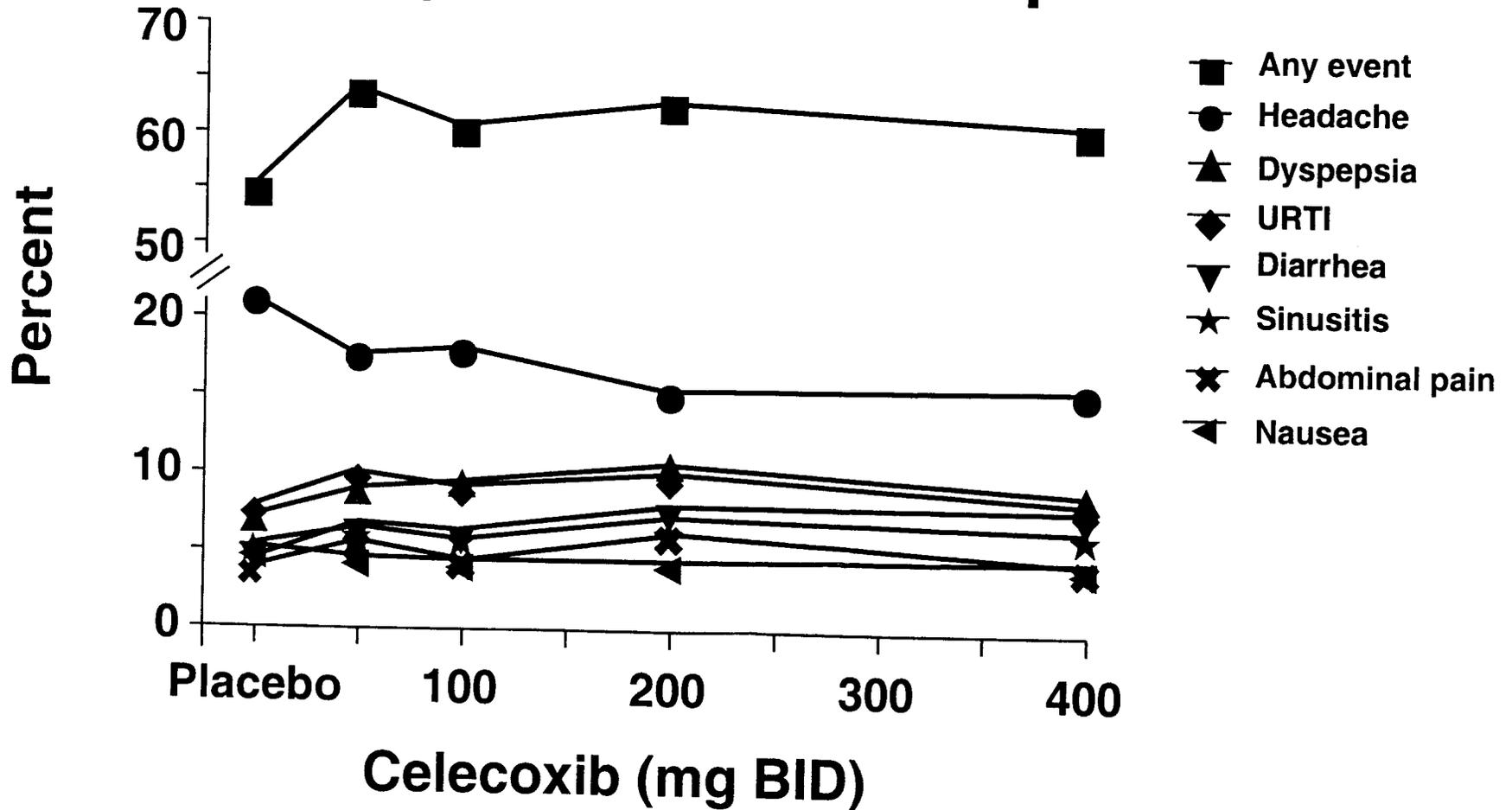
† Patients who received either celecoxib 100 mg BID, 200 mg BID or 200 mg QD

* Significantly different from placebo; $p < 0.05$

** Significantly different from celecoxib 100 mg BID, 200 mg BID or 200 mg QD; $p < 0.05$

North American Arthritis Trials

Adverse Events with Incidence $\geq 5\%$ in Any Treatment Group



0 mg: n=1864; 50 mg: n=690; 100 mg: n=1779; 200 mg: n=1914; 400 mg: n=615

Celecoxib Differentiation from NSAIDs OA/RA NDA Trials

- **Gastrointestinal**
 - **Reduction in endoscopic ulcers and ulcer-related complications compared to NSAIDs, and similar to placebo**
 - **Reduction in upper GI symptoms compared to NSAIDs**
- **Hemostasis**
 - **No effect on platelet function**

Methods - FAP Trial

- **Safety data collection**
 - **Unsolicited reports**
 - **Standardized patient questionnaire**
 - **Clinical laboratory tests**
- **NCI Common Toxicity Criteria (CTC) used to grade adverse events**

Patient Disposition

	Placebo	Celecoxib		Total
		100 mg BID	400 mg BID	
Total entered	17	34	32	83
Reasons for stopping				
Non-compliance	0	1	0	1
Lost to follow-up	0	1	0	1
Adverse Event	0	0	1	1
Serious Adverse Event	0	1	1	2
Completed Study	Ta	31	30	78 (94%)

Serious Adverse Events

Patient	Study Medication	Study Day at Onset	Description	Investigator Attribution	Completed Study
5018	100 mg BID celecoxib	104	Suicide in patient with psychiatric history	Unrelated	No
5027	400 mg BID celecoxib	94	Episode of acute allergic reaction (urticaria and minimal respiratory distress) in patient with h/o urticaria; treated as outpatient	Probably related	No
5039	100 mg BID celecoxib	20	Hospitalization for an unrelated elective resection of a pre-existing angiofibroma	Unrelated	Yes

Adverse Events FAP Study

Adverse Events	Celecoxib		
	Placebo N = 17	100 mg BID N = 34	400 mg BID N = 32
Grade 2 (various)	11 (65%)	18 (53%)	17 (53%)
GI	5 (29%)	9 (27%)	9 (28%)
Abdominal pain	2 (12%)	-	2 (6%)
Diarrhea	2 (12%)	7 (21%)	4 (13%)
Dyspepsia	-	-	1 (3%)
Melena	-	-	1 (3%)
Nausea	-	3 (9%)	-
Rectal spotting	1 (6%)	-	-
Rectal pain/burning	1 (6%)	-	1 (3%)
Stool abnormal	-	-	1 (3%)
Vomiting	1 (6%)	1 (3%)	1 (3%)
Grade 3 or greater (various)	-	2 (6%)	1 (3%)

Laboratory Tests

- **No differences between celecoxib and placebo groups**
 - **Hematology [e.g., hemoglobin/hematocrit/WBC/platelet count]**
 - **Clinical chemistry [e.g., BUN/Cr/LFT]**
 - **Urinalysis**

Celecoxib Safety Summary

- **No significant differences between celecoxib and placebo groups**
- **Celecoxib well tolerated in FAP setting consistent with larger OA/RA experience**

Overall Study Conclusions

- **Celecoxib 400 mg BID in patients with FAP:**
 - **Safe and effective treatment**
 - **Reduction and regression of colorectal polyps**
 - **Benefit in the duodenum**

FAP Follow-up Study Discussion Points

- **Objectives**
- **Study Population**
- **Endpoints**
- **Design Options**
- **Proposed Study Design**
- **Sample Size Assumptions**

FAP Follow-up Study Objectives

- **Fulfill NCI and Searle's commitment to patients with FAP and to this field**
- **Fulfill Subpart H requirements as discussed with the FDA**

Follow-up FAP Study Potential Study Population - Considered

- **Established disease - similar to population in the current study**
 - **Possible Endpoints**
 - **Composite clinical events endpoint**
 - **Secondary (subsequent) surgery**
 - **Duodenal disease**

Follow-up FAP Study Potential Study Population - Proposed

- **Pre-phenotypic disease**
 - **Endpoint**
 - **Primary (prophylactic) surgery**
- **Goal to have patient complete adolescence prior to surgical intervention for reasons of:**
 - **Physical growth**
 - **Psychological development**

FAP Follow-up Study Proposed Study Population

- **Adolescents**
 - **12 to 19 years of age**
 - **Genetic diagnosis of FAP**
 - **No phenotypic disease**
 - **No prior colorectal surgery**

Follow-up FAP Study Endpoints

- **Primary**
 - Proportion of patients that reach age 21 prior to colorectal surgery
(Leeds Castle International Polyposis Group Guideline)
- **Supportive**
 - Time to phenotypic expression
 - Time to recommendation for surgery
 - Extent of disease - gross and histopathologic
 - Number of polypectomies
 - Healthcare resource utilization and QOL

FAP Follow-up Study Design Options

- **Single arm**
 - **Comparison to historical data**
 - **Reduction of polyp development as an internal control**
- **Two arms**
 - **Placebo control**
 - **Two doses of celecoxib**

FAP Follow-up Study

Comparator - Placebo vs Active Control

- **Use of placebo control**
 - **Patient/family acceptance given results of initial celecoxib FAP study**
 - **Willingness of patients to continue on study if polyp burden increases**
 - **Physician acceptance of randomization**
- **Use of Celecoxib at two dose levels**
 - **All patients receive active agent**

Follow-up FAP Study Proposed Trial Design

- Description:** Double-blind, controlled study of celecoxib in individuals with genetically diagnosed FAP and no phenotypic disease
- Treatment Groups:** Celecoxib 100 mg BID
Celecoxib 400 mg BID
- Subjects:** N = 322 (161:161) planned
Age 12 - 19 (Stratification variable)
- Duration of Therapy:** Until need for prophylactic colorectal surgery or age 21
- Endpoint:** Proportion of patients requiring surgery prior to age 21

Follow-up FAP Study (Active Celecoxib Control) Sample Size Assumptions

- **N = 322 patients (161 - 100 mg celecoxib BID and 161 - 400 mg celecoxib BID)**
- **Historic rate: 80% have surgery by age 21 (Wu JS, Annals of Surgery 227(1):57-62, 1998 and Strang-Cornell experience)**
- **Celecoxib 100 mg BID rate: 72% have surgery by age 21 (10% drug effect)**
- **Celecoxib 400 mg BID rate: 55% have surgery by age 21 (30% drug effect)**
- **Dropout rate of 15%**
- **Power = 80%; $p = 0.05$, two-tailed**
- **Independent DSMB to monitor study and conduct interim analysis to assess assumptions**

FAP Follow-up Study Summary

- **Proposed trial design outlined**
 - **Fulfill NCI and Searle's commitment**
 - **Fulfill Subpart H requirements**

Conclusions

Philip Needleman, Ph.D.
Co-President, Searle
Chief Scientist, Monsanto

Conclusions

- **Celecoxib, 400 mg BID, is safe and effective for the reduction and regression of adenomatous colorectal polyps in patients with FAP, in conjunction with usual care**
- **Celecoxib shows a consistent benefit throughout the GI tract**
- **Celecoxib is well tolerated in patients with FAP**
- **Commitment to follow-up study**