FDA Arthritis Advisory Committee Meeting
April 12, 2007

ARCOXIA (Etoricoxib) 30 and 60 mg
for Symptomatic Treatment of Osteoarthritis

Merck Research Laboratories (MRL)

Proposed Indication and Dosing

- Proposed indication
  - *ARCOXIA is indicated for the relief of the signs and symptoms of osteoarthritis.*
- Proposed dosing
  - *The recommended dose of ARCOXIA is 30 mg or 60 mg once daily. The recommended initial dose is 30 mg once daily. Some patients may receive additional benefit from 60 mg daily versus 30 mg daily.*

Etoricoxib: A New Treatment Option

- Patients with osteoarthritis need additional treatment options
- Etoricoxib represents a valuable treatment that addresses this unmet need
- Well-established benefit to risk profile in patients for whom NSAID class therapy is indicated
  - Non-narcotic providing pain relief, improvement in physical functioning
  - Improved GI safety, tolerability in comparison to traditional NSAIDs, including in patients on a proton pump inhibitor
  - Thrombotic CV safety profile extensively characterized and consistent with non-naproxen NSAIDs

Agenda

- Introduction ..... Scott H. Korn, MD
  Executive Director,
  Regulatory Affairs, MRL
- Unmet Medical Need in OA ..... Grant W. Cannon, MD
  Professor of Medicine,
  U of Utah Division of Rheumatology
- Efficacy & Safety Review ..... Sean P. Curtis, MD
  Executive Director,
  Clinical Research, MRL

Consultants

Christopher P. Cannon, MD, FACC†	Senior Investigator, TIMI Study Group Brigham & Women's Hospital
Marc C. Hochberg, MD, MPH	Professor of Medicine Head, Div. of Rheumatology & Clinical Immunology University of Maryland School of Medicine
Richard H. Hunt, FRCP, FRCPC	Professor of Medicine & Gastroenterology McMaster University Health Science Center
Loren A. Laine, MD†	Professor of Medicine Division of Gastroenterology Keck School of Medicine University of Southern California
Samy Suissa, PhD	Professor of Epidemiology & Biostatistics McGill University

† Co-chairs of MEDAL Steering Committee.

Etoricoxib Presentation Overview

- Review of Efficacy in OA
- Review of Safety
  - Thrombotic Cardiovascular (CV)
  - Upper Gastrointestinal (GI)
  - Renovascular
- Overview of Proposed Post-Approval Activities
- Summary

Summary of Presentation

- Efficacy in osteoarthritis: Comparable to NSAIDs
- Thrombotic cardiovascular safety: Difference in favor of naproxen; comparable to diclofenac
  - Profile consistent with prior randomized clinical trials of COX-2 selective vs. traditional NSAIDs
- Gastrointestinal safety, tolerability: Superior to traditional NSAIDs
  - Etoricoxib reduced upper GI events vs. diclofenac, even in patients on proton pump inhibitors
- Renovascular safety
  - Dose-related effects on blood pressure
    - Etoricoxib 30, 60 mg between the effects observed with traditional NSAIDs
- Overall benefit to risk favorable for etoricoxib 30 and 60 mg in treatment of OA
  - Based on extensive development program (~60,000 total patient years), including a long-term cardiovascular outcomes program

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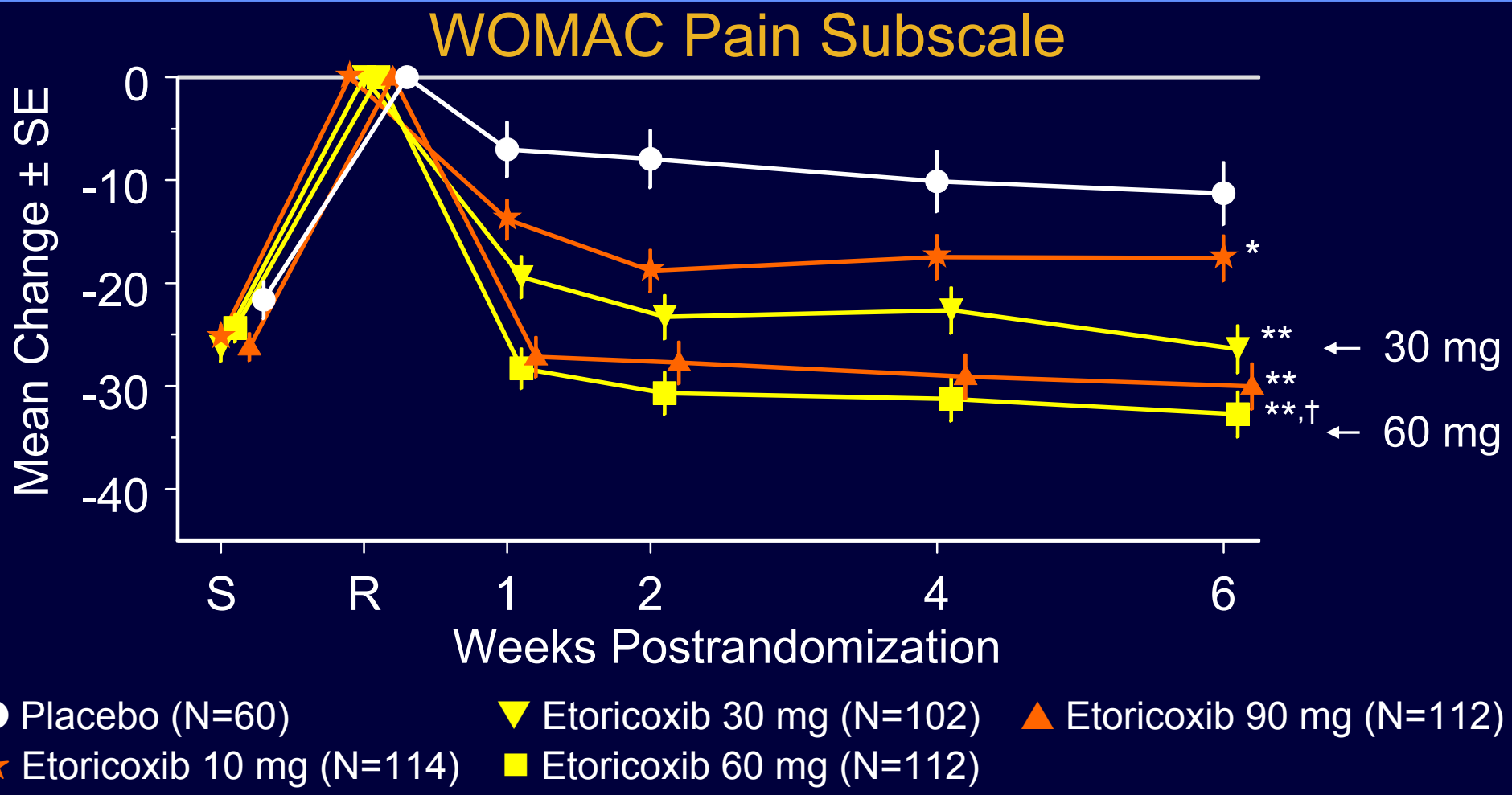
Etoricoxib OA Efficacy Studies

- 7 clinical studies (N=3897)
  - 1 dose-ranging study
  - 6 Phase III studies
    - 2 studies: Etoricoxib 60 mg vs. naproxen 500 mg BID
    - 4 studies with etoricoxib 30 mg
      - 2 vs. ibuprofen 800 mg TID
      - 2 vs. celecoxib 200 mg qD
- Standardized design, methodology
  - All randomized, double-blinded, placebo- and/or active comparator-controlled
  - Flare design in patients with OA of hip and/or knee
  - Validated endpoints covering domains of pain, function; global assessments also included

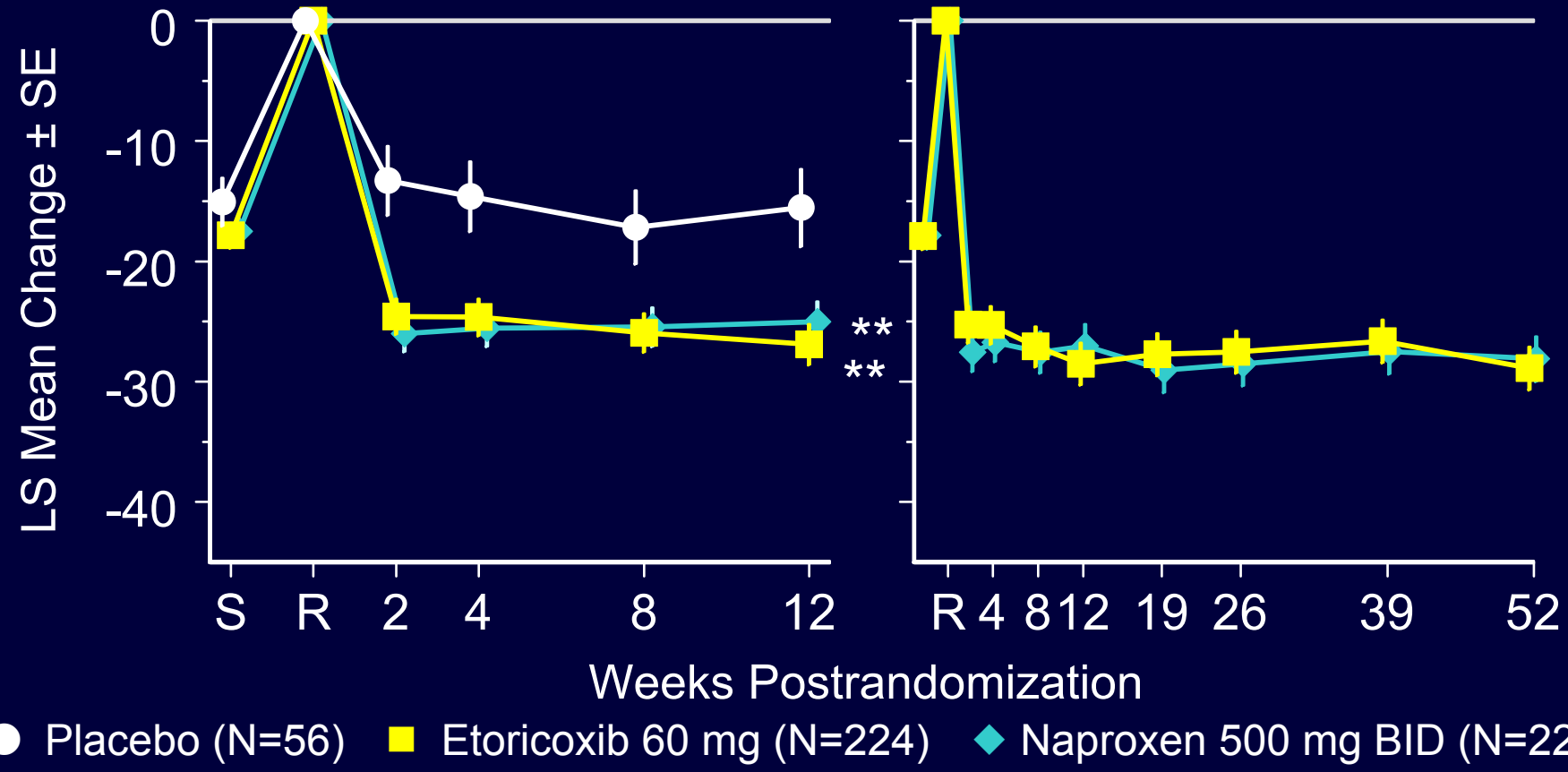
OA Dose-Ranging Study: 60 mg More Effective Than 30 mg



S = screening; R = randomization.
* p<0.050; ** p<0.001: compared with placebo; † p<0.050 etoricoxib 60 mg compared with etoricoxib 30 mg.

Etoricoxib 60 mg Comparable to Naproxen 1000 mg

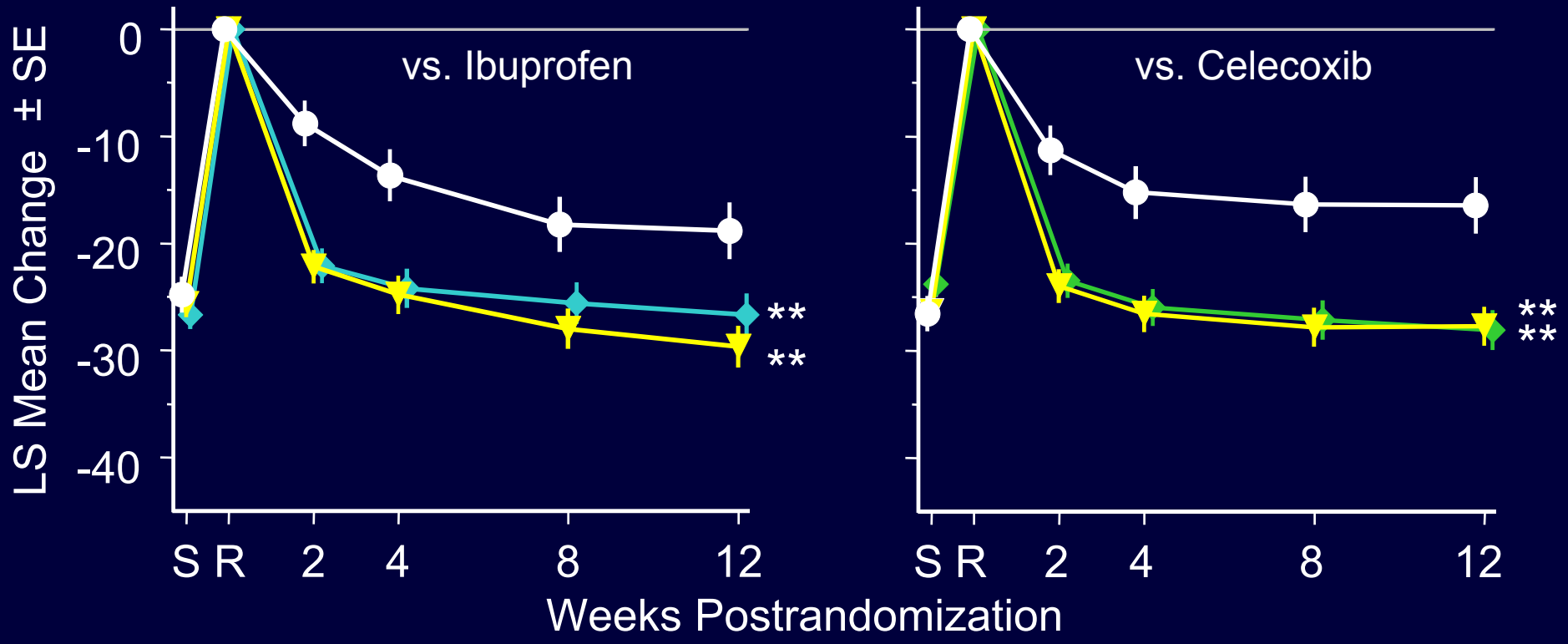
WOMAC Pain Subscale (1 of 2 Studies Displayed)



Screening (S) to baseline (R) = NSAID washout period; SE = standard error.
** p<0.001 compared with placebo.

Etoricoxib 30 mg Comparable to Ibuprofen 2400 mg and Celecoxib 200 mg

WOMAC Pain Subscale (1 of 2 Studies vs. Each Comparator Displayed)



- Placebo (N=221)
- Etoricoxib 30 mg (N=458)
- Celecoxib 200 mg (N=247)
- Ibuprofen 2400 mg (N=210)

S = screening; R = randomization.
** p<0.001: compared with placebo.

Etoricoxib is Effective for OA Symptoms

- Etoricoxib 30 mg once daily provides efficacy
  - Superior to placebo
  - Comparable to ibuprofen 2400 mg, celecoxib 200 mg
  - Clinically important improvements in multiple domains
    - Pain (WOMAC pain subscale)
    - Physical function (WOMAC physical function subscale)
    - Global assessments (patient and physician perspectives)
- Etoricoxib 60 mg provides greater efficacy compared to 30 mg
- Etoricoxib 60 mg comparable to naproxen 1000 mg

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2006 Meta-analysis of Randomized Clinical Trials: Results Consistent With 2005 FDA Conclusions

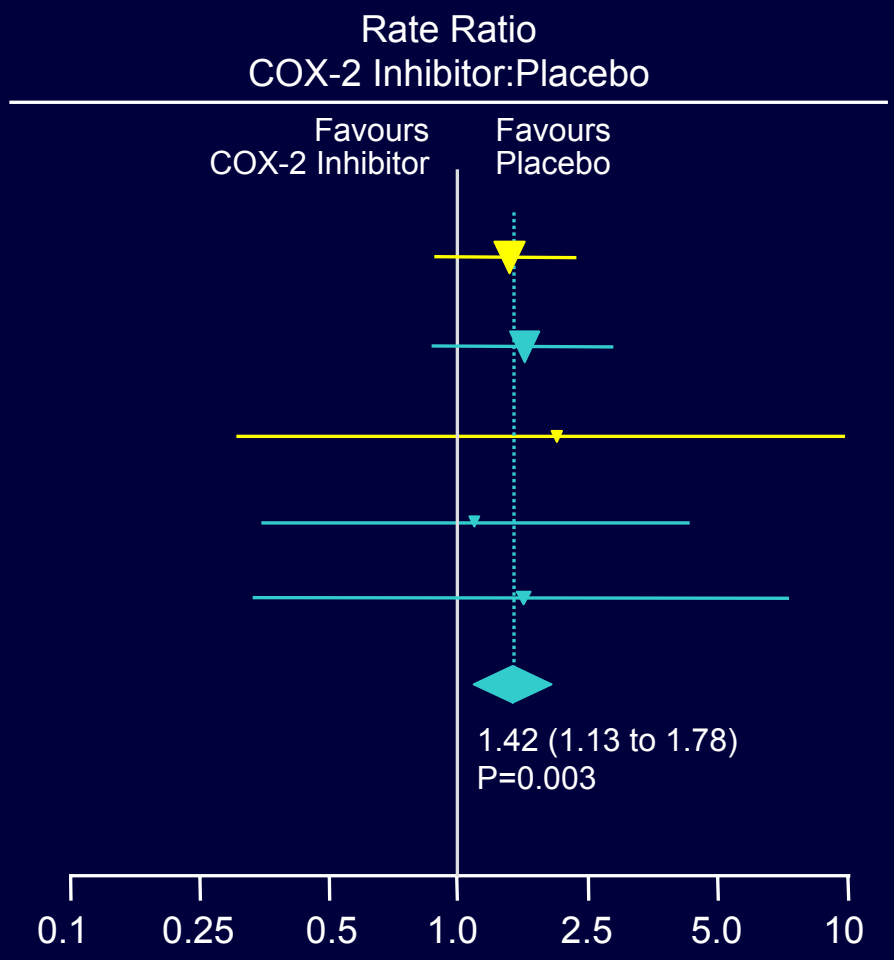
- 2005: FDA issued memo† on CV risk of NSAIDs, concluding "...*the available data are best interpreted as being consistent with a class effect of an increased risk of serious adverse CV events for COX-2 selective and non-selective NSAIDs"*
  - Naproxen a possible exception
- 2006: Meta-analysis of published and unpublished tabular data from randomized trials‡
- Methodology: Included studies ≥4 weeks duration comparing
  - COX-2 selective NSAID to placebo
    - COX-2 selective NSAIDs: Rofecoxib, celecoxib, etoricoxib, lumiracoxib, valdecoxib
  - COX-2 selective NSAID to traditional NSAID
    - Traditional NSAIDs: Naproxen, diclofenac, ibuprofen
- Endpoints: Vascular events, myocardial infarction, stroke, vascular death

† April 2005 FDA Memo; see FDA Briefing Document for April 12, 2007 Advisory Committee Meeting.
‡ Kearney P, et al. *BMJ* 2006;332:1302-1308.

Meta-analysis: COX-2 Selective NSAIDs With Moderate Increased CV Risk vs. Placebo

COX-2 Inhibitor	Events/Person Years: Allocated COX-2 Inhibitor	Events/Person Years: Allocated Placebo
Vascular Events		
Rofecoxib	98/6638	72/6415
Celecoxib	84/8976	29/4953
Etoricoxib	7/753	2/414
Lumiracoxib	14/1375	6/584
Valdecoxib	13/748	3/273
Subtotal	216/18,490	112/12,639
	(1.2%/year)	(0.9%/year)

Heterogeneity between five drugs: χ^2=0.5, df=4, P=1.0

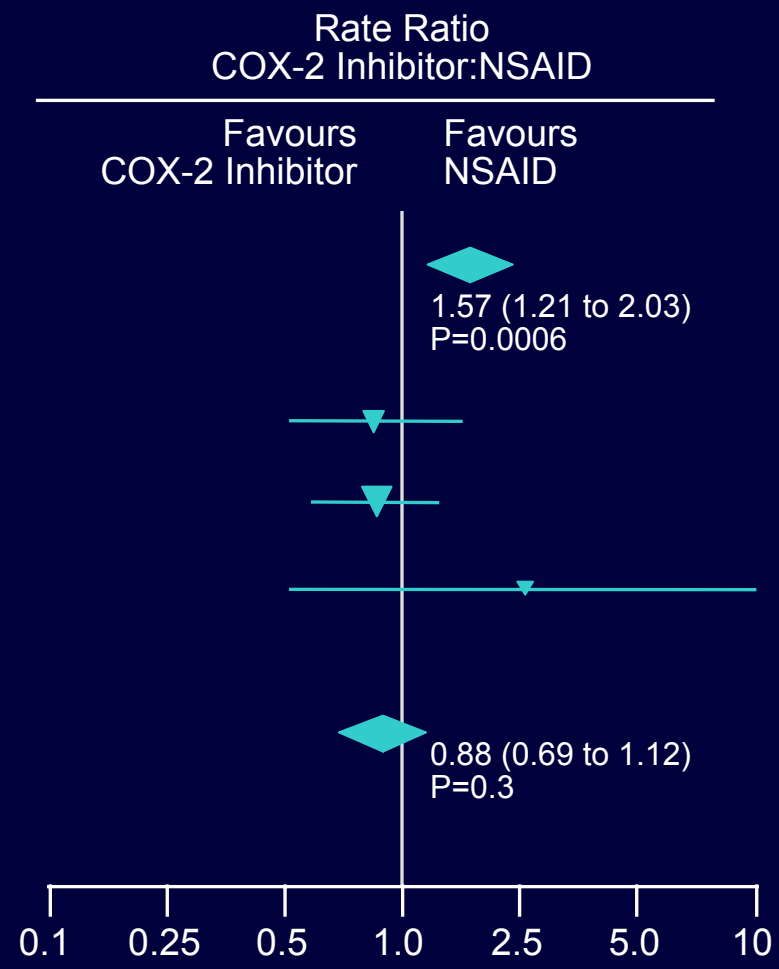


Reproduced from Kearney, et al. *BMJ* 2006;332:1302-1308.

Meta-analysis: Compared to COX-2 Selective NSAIDs, Naproxen With Lower Risk, Ibuprofen and Diclofenac With Similar Risk

COX-2 Inhibitor Versus:	Events/Person Years: Allocated COX-2 Inhibitor	Events/Person Years: Allocated NSAID
Vascular Events		
(a) Naproxen	185/16,360 (1.1%/year)	81/10,978 (0.7%/year)
Ibuprofen	46/5848	47/5160
Diclofenac†	101/10,886	79/6913
Other Non-naproxen	8/166	4/274
(b) Any Non-naproxen	155/16,900 (0.9%/year)	130/12,347 (1.1%/year)

Heterogeneity between (a) and (b): χ^2=10.2, df=1, P=0.001
Between non-naproxen NSAIDs: χ^2=2.6, df=2, P=0.3



Adapted from Kearney, et al. *BMJ* 2006;332;1302-1308.
† Does not include MEDAL and EDGE II data as studies ongoing.

Two Complementary Evaluations of Etoricoxib Safety

- Etoricoxib Development Program (N=10,033): 1998-2005
  - Primarily a comparison to naproxen 1000 mg
  - Includes assessments of upper GI, thrombotic CV safety
  - Etoricoxib doses ranging from 30-120 mg
- MEDAL Program (N=34,701): 2002-2006
  - Event-driven CV outcomes program comparing etoricoxib to diclofenac 150 mg
  - Etoricoxib doses 60 and 90 mg
  - 3 component studies
    - EDGE
    - EDGE II
    - MEDAL

Etoricoxib Development Program: Provides Thrombotic CV, GI Safety Data Primarily vs. Naproxen

- 18 studies in Etoricoxib Development Program N=10,033
  - 11 studies in OA Development Program N=5,708
    - 7 efficacy studies
    - 4 additional studies in OA
  - 3 additional studies in RA N=2848
    - 1 dose-ranging study
    - 2 Phase III studies
    - RA data from OA/RA Endoscopy Study
  - 3 studies in Chronic Low Back Pain N=1090
  - 1 study in Ankylosing Spondylitis N=387
- Majority (63%) of data from naproxen-controlled studies

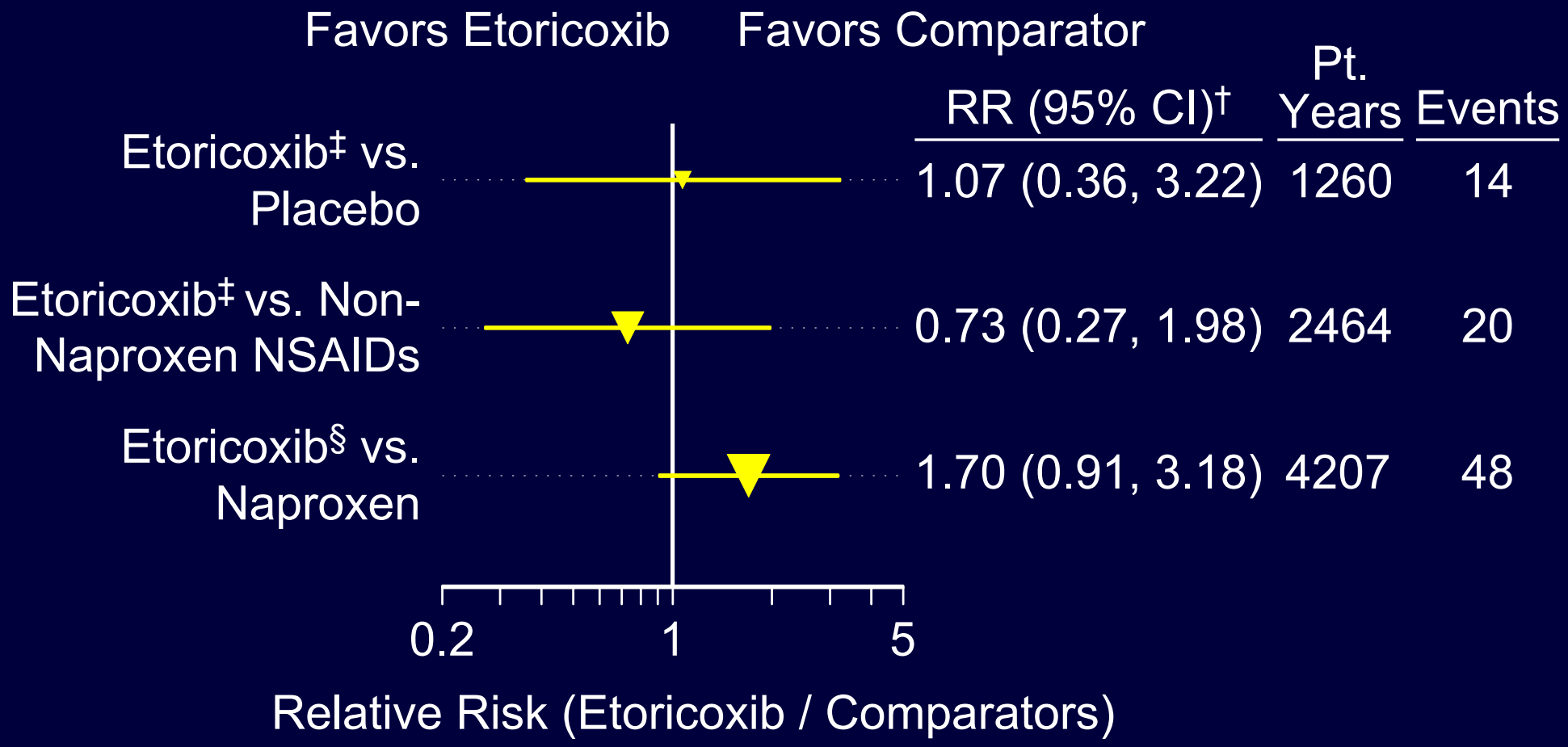
Etoricoxib Development Program: Description of Thrombotic CV Analysis

- Pooled analysis of individual patient data from 18 studies
  - All studies ≥4 weeks in duration
- Comparisons of etoricoxib (doses pooled, 30-120 mg) vs.:
  - Placebo
  - Naproxen 1000 mg
    - Rationale for comparing etoricoxib to naproxen separately
      - Pharmacodynamically distinct in its antiplatelet effect
  - Nonselective NSAIDs combined excluding naproxen
    - Diclofenac 150 mg, ibuprofen 2400 mg
- Primary Endpoint: Confirmed Thrombotic CV Events
  - Composite of cardiac, cerebrovascular, peripheral arterial and venous thrombotic events
  - Analysis approach: All events through 14 days following last dose of therapy

Etoricoxib Development Program Thrombotic CV Analysis Datasets: Naproxen-Controlled Dataset the Largest

	Placebo-Controlled		Non-Naproxen NSAID-Controlled		Naproxen-Controlled	
	Etoricoxib	Placebo	Etoricoxib	Non-Naproxen NSAIDs	Etoricoxib	Naproxen
Patients	3940	2337	2147	1470	1960	1497
Median Duration (Months)	2.8	2.8	3.3	3.2	12.5	11.3
Patient-Years	810	450	1815	649	2480	1727
Mean Etoricoxib Dose (mg/Day)	72		78		89	

Etoricoxib Development Program Thrombotic CV Events: Naproxen Trends Lower than Etoricoxib, Etoricoxib Similar to Non-Naproxen NSAIDs



† mITT approach (events within 14 days); ‡ Pooled 30-120 mg; § Pooled 60-120 mg.

MEDAL Program: Introduction

- 2002: Program initiated to compare thrombotic CV safety profile of etoricoxib to a traditional NSAID in arthritis patients
- Single, active comparator chosen
  - Single comparator provides greater precision
  - Placebo arm not reasonable in long-term trial of arthritis patients
- Primary hypothesis: Etoricoxib will demonstrate non-inferior CV safety to diclofenac
  - Primary endpoint: Confirmed thrombotic CV events
  - Endpoint-driven; at least 635 endpoints required
  - Upper bound of 95% CI for hazard ratio must be less than 1.30
  - Per-protocol population used for primary analysis
    - Intention-to-treat analyses performed to demonstrate consistency

MEDAL Program Designed in 2002

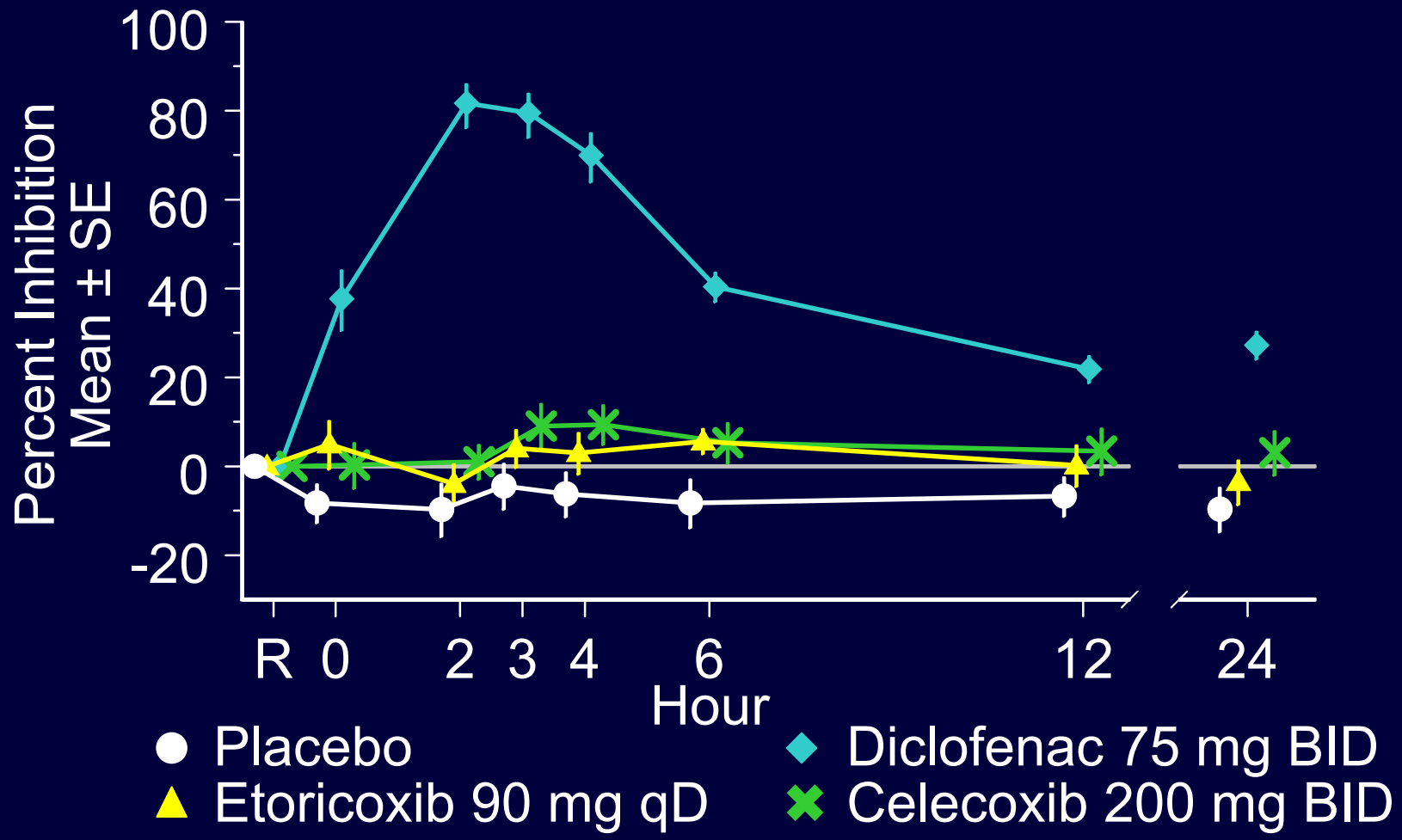
Diclofenac Chosen as Comparator

- Most widely prescribed NSAID worldwide
- Does not interfere with antiplatelet effects of aspirin (ASA)
  - >25% of MEDAL Program patients anticipated to require low-dose ASA
- Traditional NSAID: Inhibits both COX-1 and COX-2 at therapeutic doses
- Other comparators considered, but not selected
  - Naproxen: Data vs. naproxen (both CV and GI) already being acquired in Etoricoxib Development Program
  - Ibuprofen: Interferes with antiplatelet effects of ASA†
    - FDA statement 2006 regarding potential for the attenuation of antiplatelet effects of ASA‡
    - Concerns about efficacy, tolerability over longer-term

† Catella-Lawson F, et al. *NEJM* 2001;345:1809-17.
‡ FDA science paper http://www.fda.gov/cder/drug/infopage/ibuprofen/science_paper.htm.

Diclofenac inhibits COX-1, Whereas Etoricoxib and Celecoxib Do Not

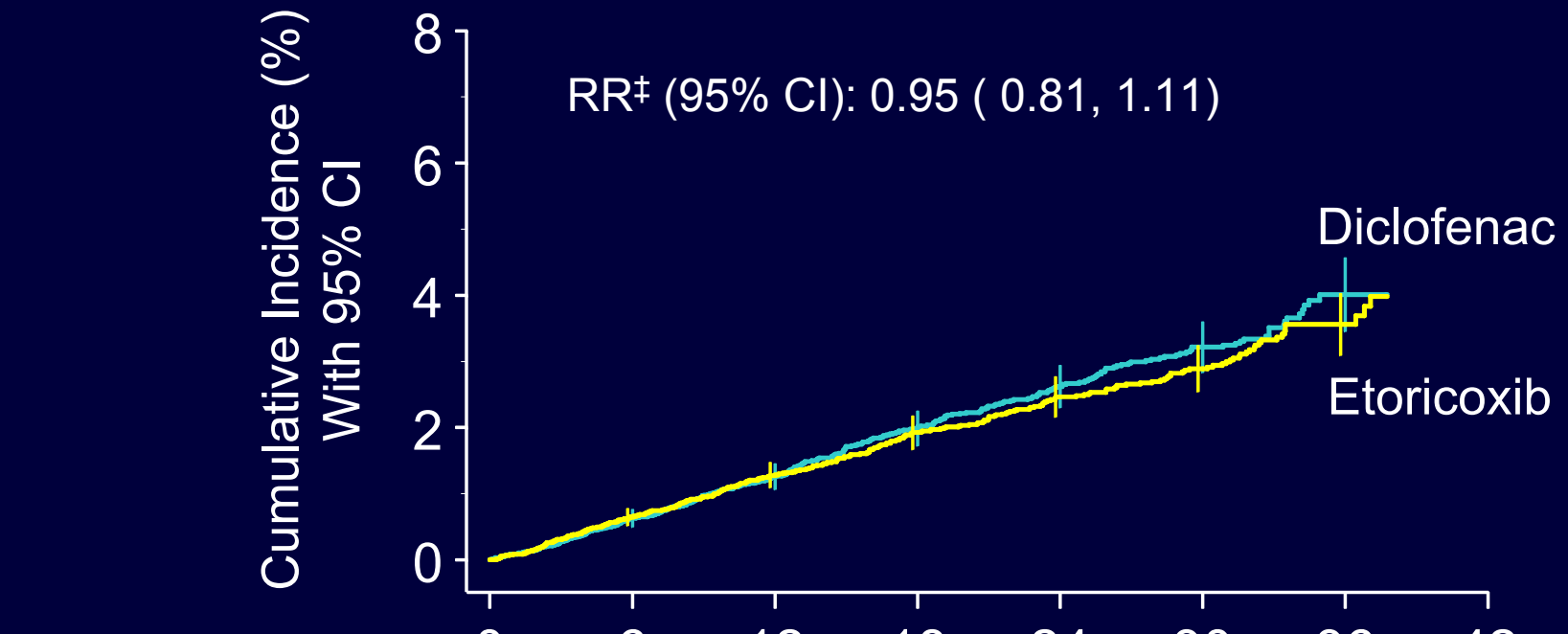
Inhibition in Serum Thromboxane, Multiple Dosing



MEDAL Program: Component Studies

	MEDAL Program	EDGE	EDGE II	MEDAL Study
Study Size	34,701	7111	4086	23,504
Patient Population	OA (72%) RA (28%)	OA	RA	OA (76%) RA (24%)
Primary Objective	CV Safety	GI Tolerability	GI Tolerability	CV Safety
Etoricoxib Dose	60 mg (OA), 90 mg (RA, OA)	90 mg	90 mg	60 mg (OA), 90 mg (RA, OA)
Mean Duration	18 mos			
Median Duration	16 mos			
Maximum Duration	42 mos			

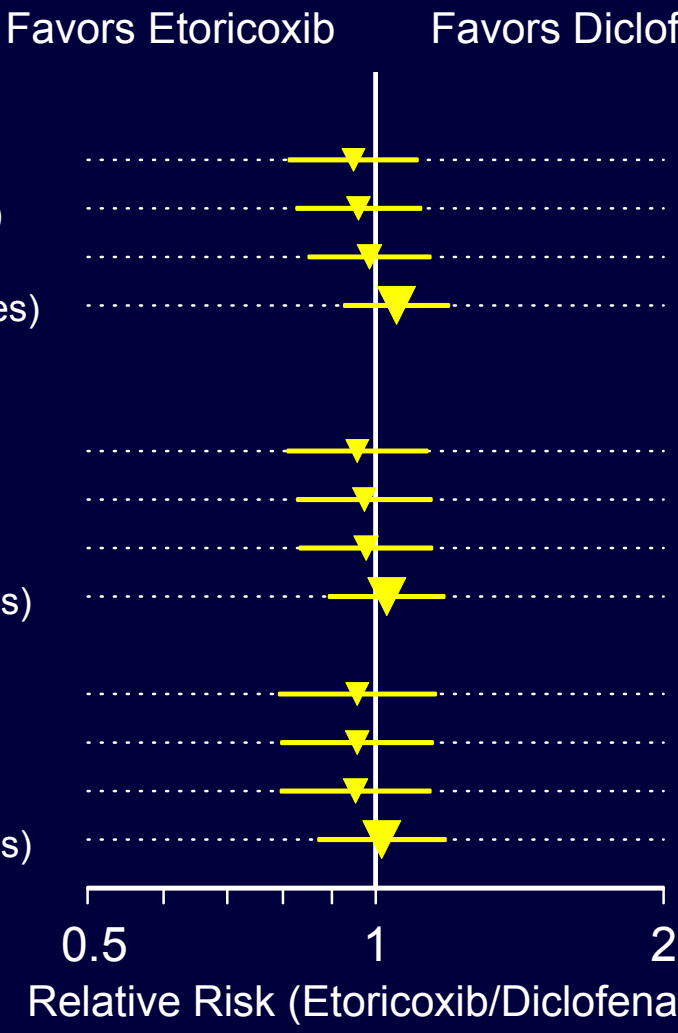
MEDAL Program: Etoricoxib Non-inferior to Diclofenac in Thrombotic CV Event Rates



# Patients at Risk								No. of Events
Etoricoxib	16819	13359	10733	8277	6427	4024	805	320
Diclofenac	16483	12800	10142	7901	6213	3832	815	323

‡ Per-protocol population.

MEDAL Program: Thrombotic CV Results Consistent Across Endpoints, Analytical Approaches



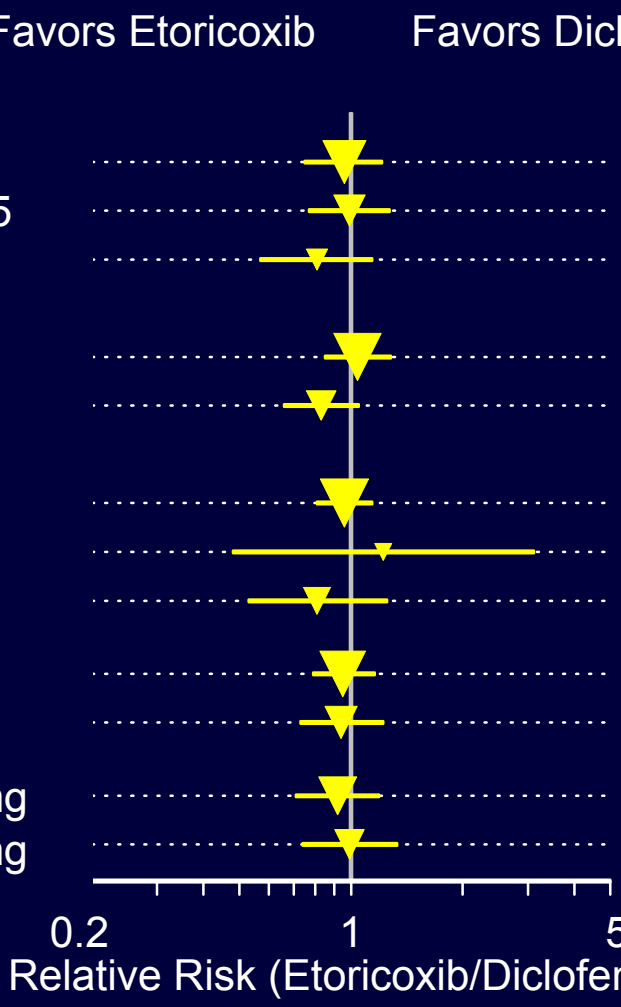
		RR (95% CI)	Pt. Years	Events
Confirmed Thrombotic Events	Per-protocol	0.95 (0.81, 1.11)	50602	643
	ITT (within 14 days)	0.96 (0.83, 1.11)	51778	690
	ITT (within 28 days	0.98 (0.85, 1.14)	53078	723
	ITT (to end of studies)	1.05 (0.93, 1.19)	79067	963
Confirmed Arterial Events	Per-protocol	0.96 (0.81, 1.13)	50610	544
	ITT (within 14 days)	0.97 (0.83, 1.14)	51785	590
	ITT (within 28 days)	0.98 (0.83, 1.15)	53089	605
	ITT (to end of studies)	1.03 (0.89, 1.18)	79280	801
Confirmed APTC	Per-protocol	0.96 (0.79, 1.16)	50638	432
	ITT (within 14 days)	0.96 (0.80, 1.15)	51818	463
	ITT (within 28 days)	0.95 (0.80, 1.14)	53128	476
	ITT (to end of studies)	1.02 (0.87, 1.18)	79518	657

MEDAL Program: No Differences Observed in MIs, Ischemic Strokes

	Etoricoxib (N=16,819)		Diclofenac (N=16,483)	
	n	Rate‡	n	Rate‡
Total Patients With Endpoint†	320	1.24	323	1.30
Cardiac Events	183	0.71	194	0.78
Non-fatal Myocardial Infarction	105	0.41	105	0.42
Fatal Myocardial Infarction	6	0.02	17	0.07
Cerebrovascular Events	89	0.34	79	0.32
Non-fatal Ischemic Stroke	53	0.21	55	0.22
Fatal Ischemic Stroke	6	0.02	2	0.01
Peripheral Vascular Events	53	0.21	55	0.22

† Per-protocol population.
‡ Events per 100 patient-years.

MEDAL Program Thrombotic CV Event Results Consistent Across Multiple Subgroups



		RR (95% CI)†	Pt. Years	Events
Age	<65	0.96 (0.75, 1.21)	31022	269
	≥65 to <75	0.99 (0.77, 1.27)	14876	243
	≥75	0.81 (0.57, 1.14)	4704	131
Gender	Female	1.04 (0.85, 1.28)	37623	367
	Male	0.83 (0.66, 1.05)	12979	276
Ethnic Group	White	0.96 (0.81, 1.14)	38726	542
	Black	1.22 (0.48, 3.11)	1713	18
	Other	0.81 (0.53, 1.25)	10162	83
Disease	OA	0.95 (0.79, 1.16)	34695	413
	RA	0.94 (0.73, 1.22)	15908	230
Dose in OA Patients	Etori 60 mg	0.92 (0.71, 1.19)	22553	233
	Etori 90 mg	0.99 (0.74, 1.33)	12142	180

† Per-protocol population.

MEDAL Program Thrombotic CV Event Results Consistent Across Range of CV Risk Factors

		RR (95% CI)†	Pt. Years	Events
History of Hypertension	Yes	1.01 (0.83, 1.23)	23286	395
	No	0.87 (0.68, 1.12)	27316	248
History of Dyslipidemia	Yes	1.00 (0.78, 1.29)	14196	241
	No	0.92 (0.75, 1.11)	36406	402
History of Diabetes	Yes	1.21 (0.81, 1.80)	5066	98
	No	0.91 (0.77, 1.07)	45537	545
Current Cigarette User	Yes	1.09 (0.76, 1.56)	6028	119
	No	0.92 (0.78, 1.09)	44575	524
Family History of CV Disease	Yes	1.13 (0.79, 1.60)	8599	127
	No	0.90 (0.75, 1.09)	37140	444
History of ASCVD	Yes	0.94 (0.70, 1.26)	5397	174
	No	0.96 (0.80, 1.15)	45205	469

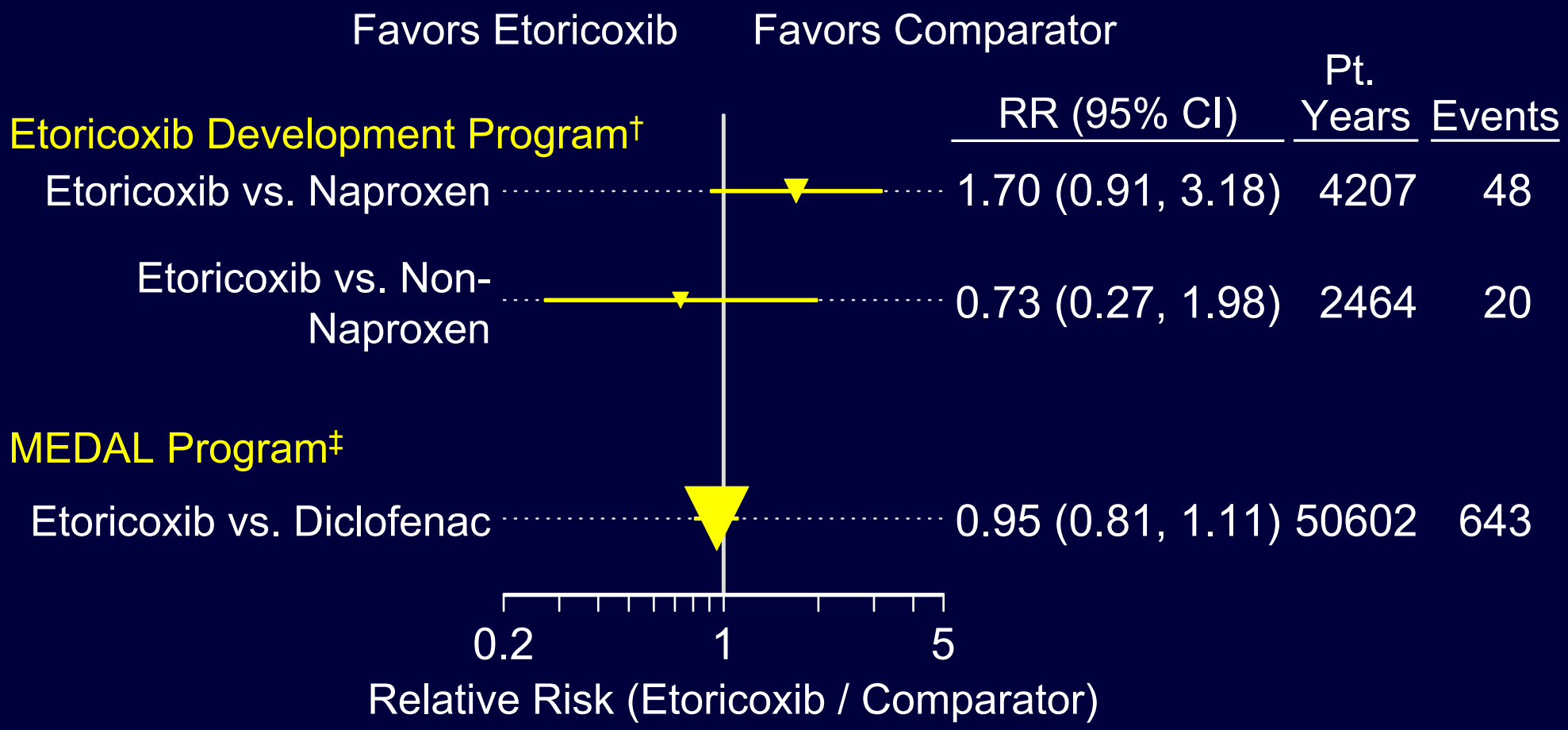
† Per-protocol population. ASCVD = atherosclerotic cardiovascular disease.

MEDAL Program Results Consistent With 2005 FDA Conclusions on NSAID CV Risk

- 2005 FDA concluded available data consistent with class effect of increased thrombotic CV events for both COX-2 selective and non-selective NSAIDs
  - Data from well-controlled observational studies have not provided consistent assessments of risk between COX-2 selective and non-selective NSAIDs
- 2006 meta-analysis of RCT data support 2005 FDA conclusion
- Observational data do not clearly establish magnitude of CV risk with diclofenac
  - Compared with non-use (McGettigan meta-analysis†), relative risk 1.4
    - Individual study estimates variable (0.8 to 1.6)
    - Statistically significant heterogeneity
    - Diclofenac data from large Medi-CAL study in 2005 (Singh‡) not included
      - RR for diclofenac ≤150 = 1.02 vs. remote use of NSAIDs
  - Compared with use of other NSAIDs, data limited to 2 studies of MI
    - 0.59 (0.32-1.08) vs. other NSAIDs; 1.33 (1.03-1.73) vs. ibuprofen
- Diclofenac remains valid comparator for MEDAL Program

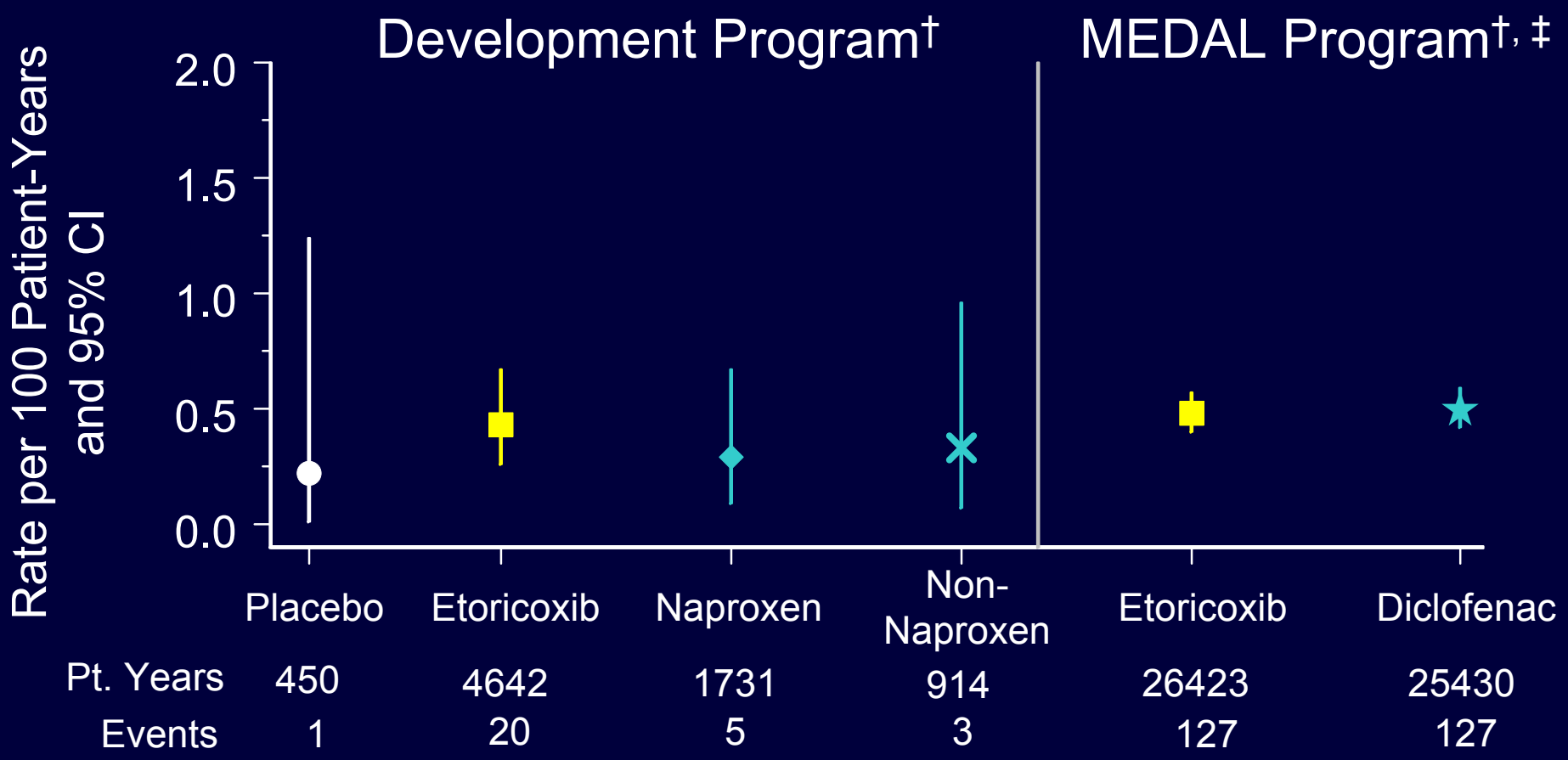
† McGettigan et al. *JAMA.* 2006;296:1633-44.
‡ Singh et al. *Ann Rheum Dis* 2005;64(Suppl III):85.

Summary Thrombotic CV Event Results: Etoricoxib Development Program and MEDAL Program



† mITT approach (events within 14 days).
‡ Per-protocol approach.

Overall Mortality: Etoricoxib Similar to Comparator NSAIDs



† All events through 14 days following last dose of therapy.
‡ Pooled MEDAL Program, Relative Risk (95% CI): 0.96 (0.75, 1.23).

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Etoricoxib Development Program Description of GI Safety Evaluation

- COX-2 biochemical assays
  - Human blood cells, gastric mucosa
- Fecal red blood cell loss study vs. placebo, ibuprofen
- Endoscopy vs. placebo, ibuprofen, naproxen
- Prespecified clinical outcomes in Etoricoxib Development Program
  - Upper GI clinical events
    - Bleeding, perforation, obstruction, ulcer diagnosed on clinical workup
    - All clinical workups 'for cause'
    - Events confirmed through blinded adjudication using prespecified criteria
  - GI tolerability analysis

Etoricoxib Development and MEDAL Programs Description of Upper GI Event Analyses

- Etoricoxib Development Program
  - Prespecified pooled analysis of individual patient data from 18 studies
  - Comparison of etoricoxib (30-120 mg) vs. combined traditional NSAIDs (naproxen, ibuprofen, diclofenac); naproxen also individually assessed
- MEDAL Program
  - Prespecified analysis based on pooled MEDAL Program data
  - Concomitant use of low-dose aspirin (LDA), proton pump inhibitors (PPI) allowed and encouraged per clinical guidelines
    - 33% of pts used LDA regularly (>75% of time on study therapy)
    - 40% of pts used PPI regularly (>75% of time on study therapy)
- Primary Endpoint: Confirmed Overall Upper GI Clinical Events
    - Investigator-reported events adjudicated by blinded, external committee according to prespecified criteria
    - Complicated upper GI events also evaluated
- Analysis approach: All events through 14 days following last dose of therapy

Upper GI Clinical Events: Determined During Evaluation Based on Clinical Signs, Symptoms

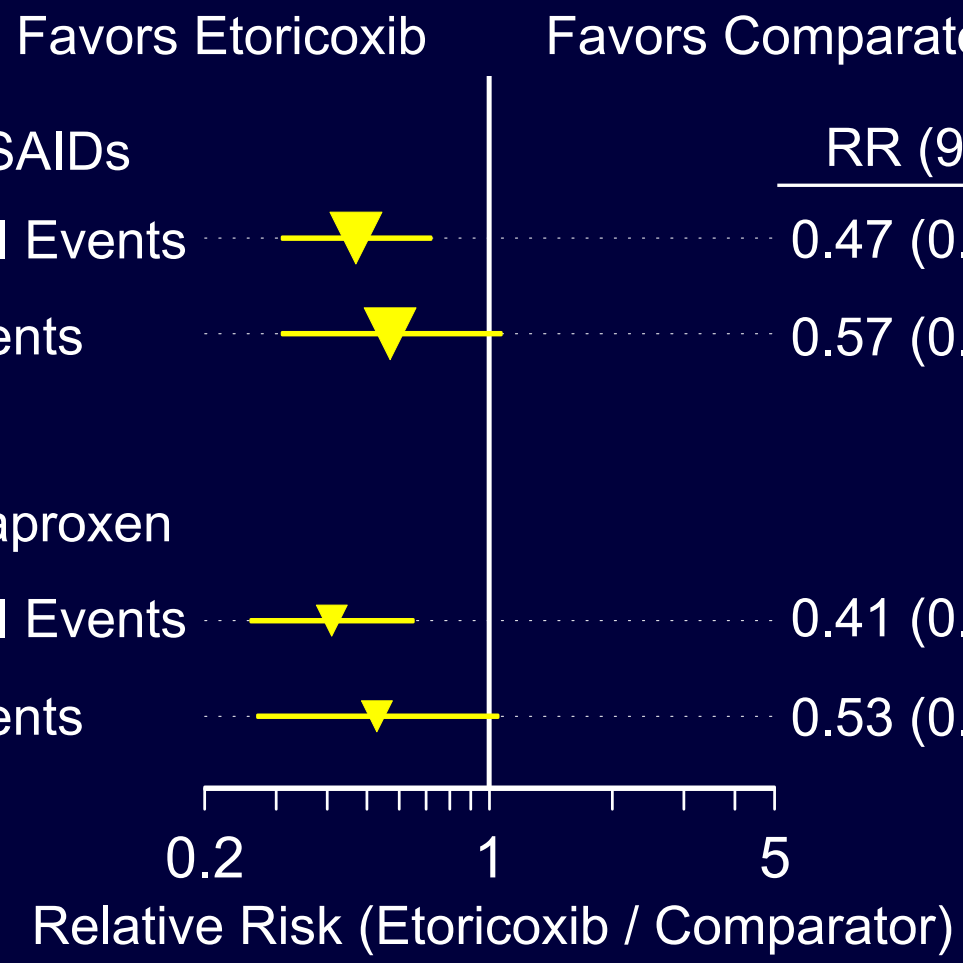
	Overall Upper GI Events	Complicated Events
Perforation	√	√
Obstruction	√	√
Bleeding		
Complicated *	√	√
Uncomplicated	√	
Ulcer	√	

* Health-care witnessed bleeding; active documented upper GI bleed; occult positive stool with significant bleeding (↓ BP, orthostatic change in HR, BP, ↓ Hgb >2 mg/L, or transfusion); Pt. reported significant bleeding.

Etoricoxib Development Program Upper GI Analysis: Description of Data Sets

	All Active Comparator-Controlled		Naproxen-Controlled Subset	
	Etoricoxib	NSAIDs	Etoricoxib	Naproxen
Patients	4107	2967	1960	1497
Median Duration (Months)	6.4	3.3	12.5	11.2
Patient-Years	4295	2373	2478	1724
Mean Etoricoxib Dose (mg/Day)	84		89	

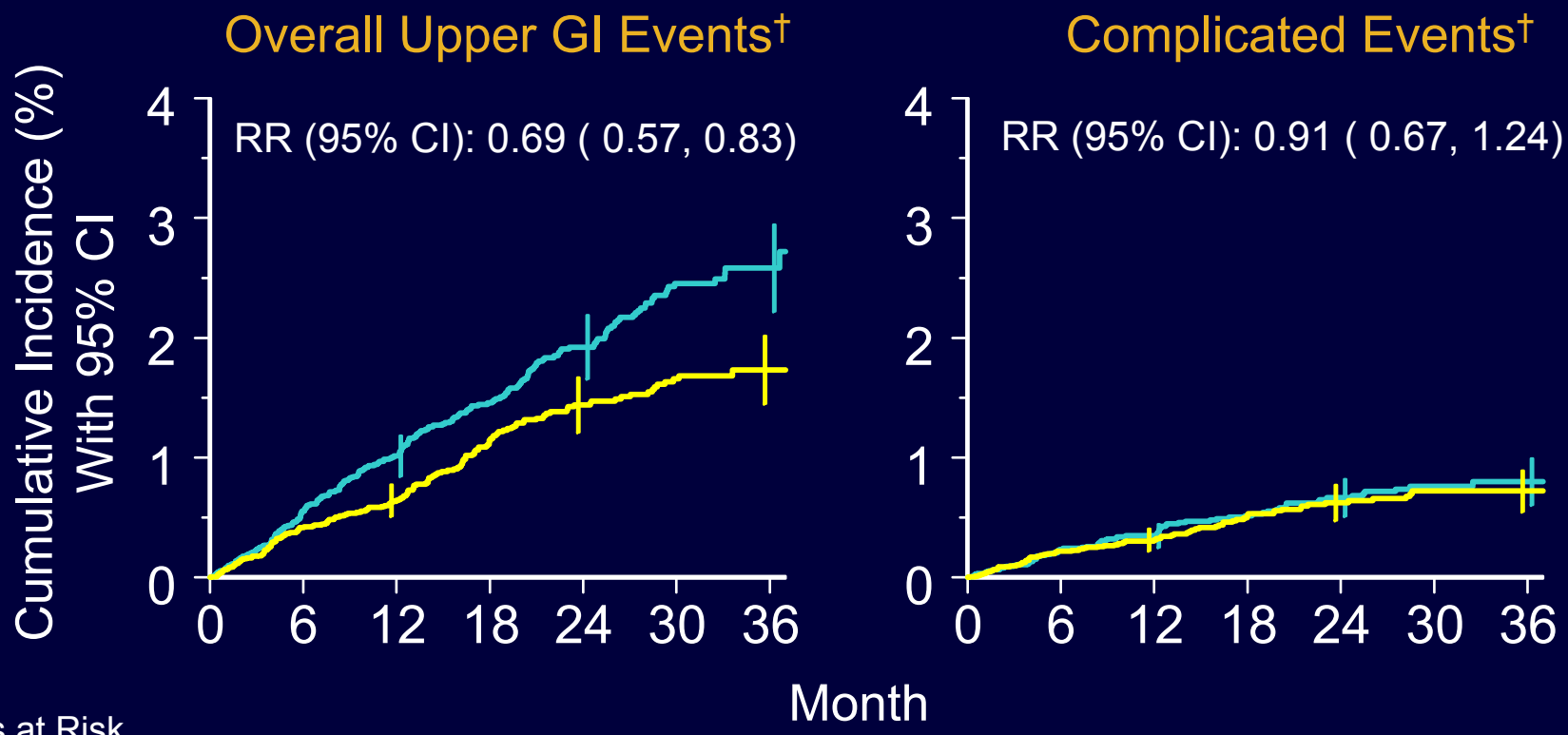
Etoricoxib Development Program: Fewer Upper GI Events With Etoricoxib



	RR (95% CI)†	Pt. Years	Events
Etoricoxib vs. NSAIDs			
Overall Upper GI Events	0.47 (0.31, 0.72)	6668	95
Complicated Events	0.57 (0.31, 1.07)	6678	42
Etoricoxib vs. Naproxen			
Overall Upper GI Events	0.41 (0.26, 0.65)	4203	79
Complicated Events	0.53 (0.27, 1.05)	4212	34

† All events through 14 days following last dose of therapy.

MEDAL Program: Significantly Fewer Overall Upper GI Events vs. Diclofenac; No Significant Difference in Complicated Events



# Patients at Risk								
Etoricoxib	17412	10972	6509	821	17412	10984	6521	822
Diclofenac	17289	10396	6306	820	17289	10406	6322	825

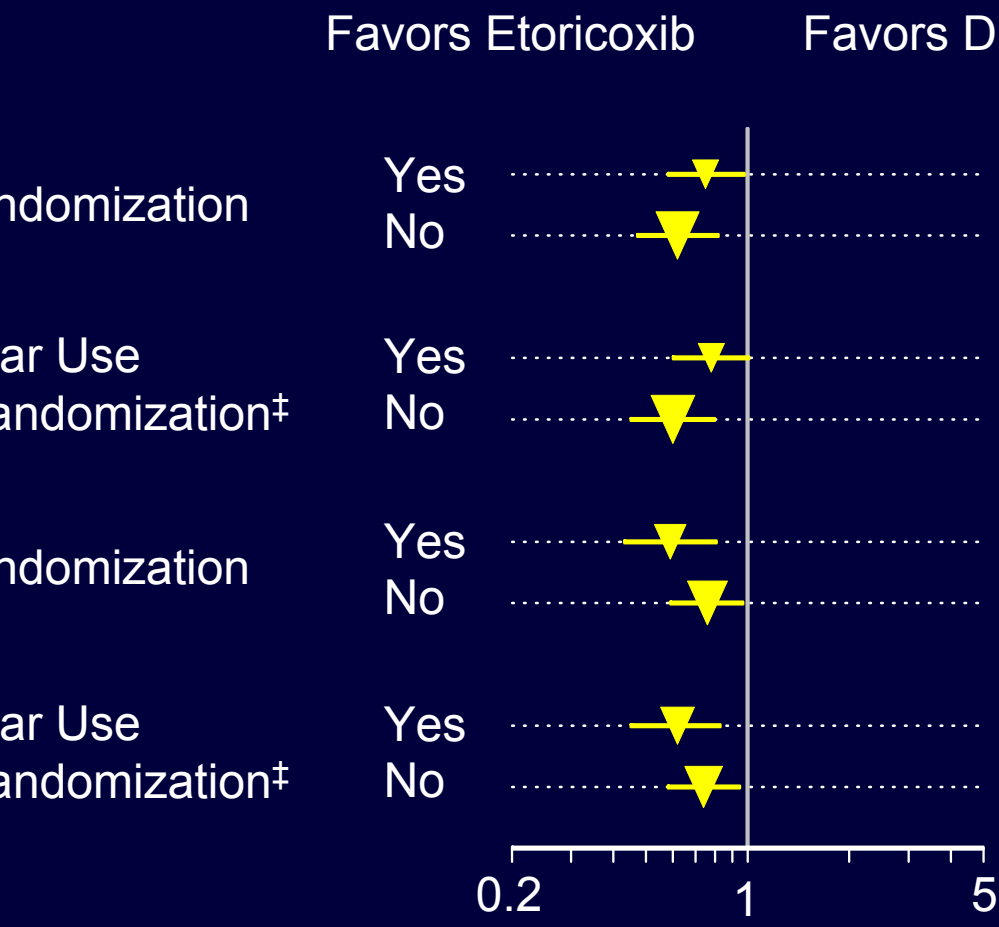
† ITT approach (events within 14 days).

MEDAL Program: Reduction in Overall Upper GI Events Due to Symptomatic Ulcer Reduction

	Etoricoxib (N=17,412)		Diclofenac (N=17,289)	
	n	Rate‡	n	Rate‡
Patients With Any Clinical Event	176	0.67	246	0.97
Patients With Complicated Events	78	0.30	82	0.32
Perforation§	5	0.02	11	0.04
Obstruction	2	0.01	2	0.01
Bleeding	72	0.27	72	0.28
Patients With Uncomplicated Events	98	0.37	164	0.65
Bleeding‖	6	0.02	4	0.02
Ulcer	92	0.35	161	0.63

‡ Events per 100 patient-years.
§ 4 patients with perforation also had bleeding reported.
‖ 1 patient with uncomplicated bleeding from Mallory-Weiss tear also had an uncomplicated gastric ulcer identified.

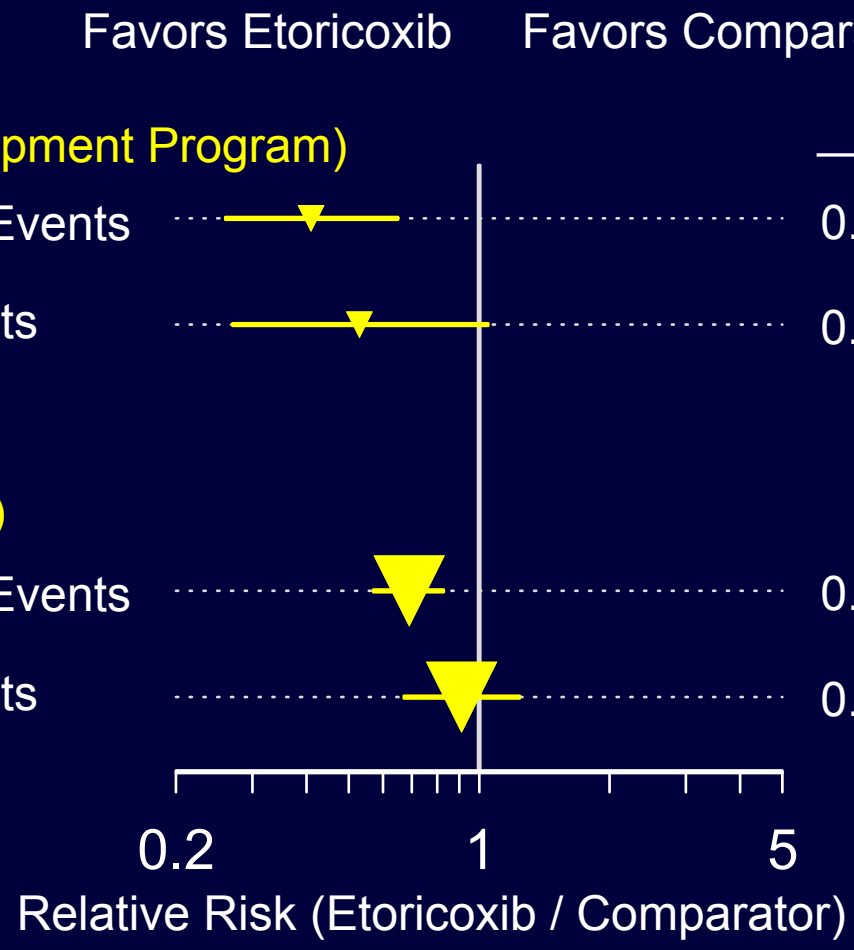
MEDAL Program: Reduction in Overall UGI Events Maintained With PPI, Aspirin Use



		RR (95% CI)†	Pt. Years	Event
ASA				
Prerandomization	Yes	0.75 (0.58,0.98)	17590	227
	No	0.62 (0.46,0.82)	34185	195
Regular Use Postrandomization‡	Yes	0.78 (0.60,1.01)	17268	224
	No	0.60 (0.45,0.80)	34506	198
PPI				
Prerandomization	Yes	0.59 (0.43,0.81)	21812	169
	No	0.76 (0.59,0.97)	29963	253
Regular Use Postrandomization‡	Yes	0.62 (0.45,0.83)	23865	174
	No	0.74 (0.58,0.95)	27910	248

† ITT approach (events within 14 days). ‡ Postrandomization use of low-dose aspirin or PPIs ≥75% of study period.
Treatment by subgroup interaction not significant. PPI=Proton pump inhibitor.

Etoricoxib Development Program and MEDAL Program: Summary of Upper GI Safety



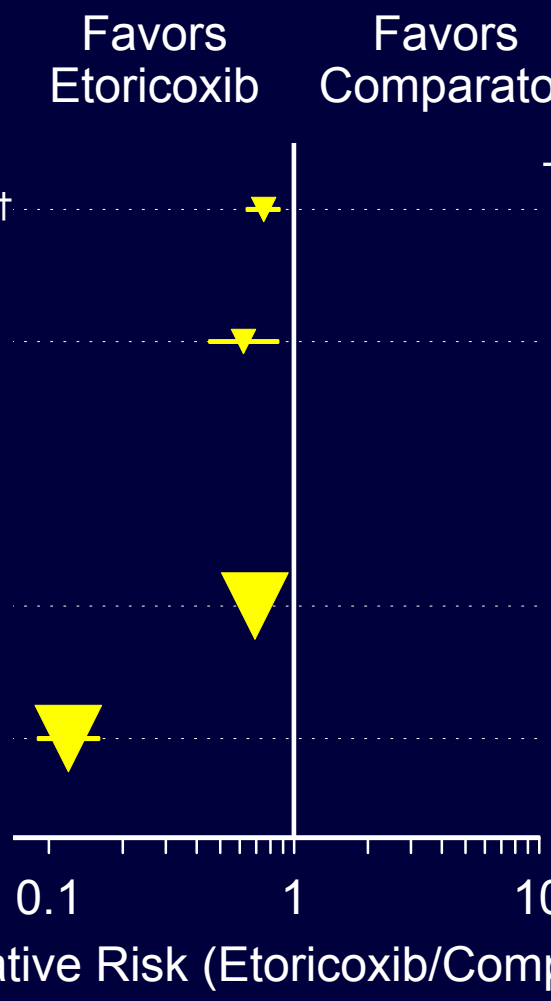
	RR (95% CI)†	Pt. Years	Events
Vs. Naproxen (Etoricoxib Development Program)			
Overall Upper GI Events	0.41 (0.26, 0.65)	4203	79
Complicated Events	0.53 (0.27, 1.05)	4212	34
Vs. Diclofenac (MEDAL Program)			
Overall Upper GI Events	0.69 (0.57, 0.83)	51775	422
Complicated Events	0.91 (0.67, 1.24)	51843	160

† All events through 14 days following last dose of therapy.

Etoricoxib Development Program and MEDAL Program: Description of GI Tolerability Analyses

- Etoricoxib Development Program
  - 2 representative prespecified endpoints presented
    - New Use of Gastroprotective Agents (GPAs)
    - Patient Discontinuation for 'NSAID-type' AEs (acid reflux, dyspepsia, epigastric discomfort, heartburn, nausea, vomiting, and abdominal pain)
  - 2 studies (endoscopy) excluded because GPAs not allowed
  - Etoricoxib (30-120 mg) vs. NSAIDs combined (naproxen, ibuprofen, diclofenac)
- MEDAL Program
  - 2 endpoints: Patient Discontinuation for Clinical GI AEs; Patient Discontinuation for Hepatic AEs
  - Comparison of etoricoxib vs. diclofenac presented based on pooled MEDAL Program for consistency
- Analysis approach: All events through 14 days following last dose of therapy

Summary of GI Tolerability: Etoricoxib Development Program and MEDAL Program



	RR (95% CI)	Pt. Years	Events
Development Program			
New Use of Concomitant GPAs†	0.75 (0.64, 0.87)	6033	716
D/C Due to NSAID-Type AEs	0.62 (0.45, 0.86)	6443	151
MEDAL Program			
D/C Due to GI Clinical AEs	0.69 (0.64, 0.75)	51161	2451
D/C Due to Hepatic AEs	0.12 (0.09, 0.16)	51161	518

D/C = patient discontinuation.
† All events through 14 days following last dose of therapy.

Etoricoxib Presentation Overview

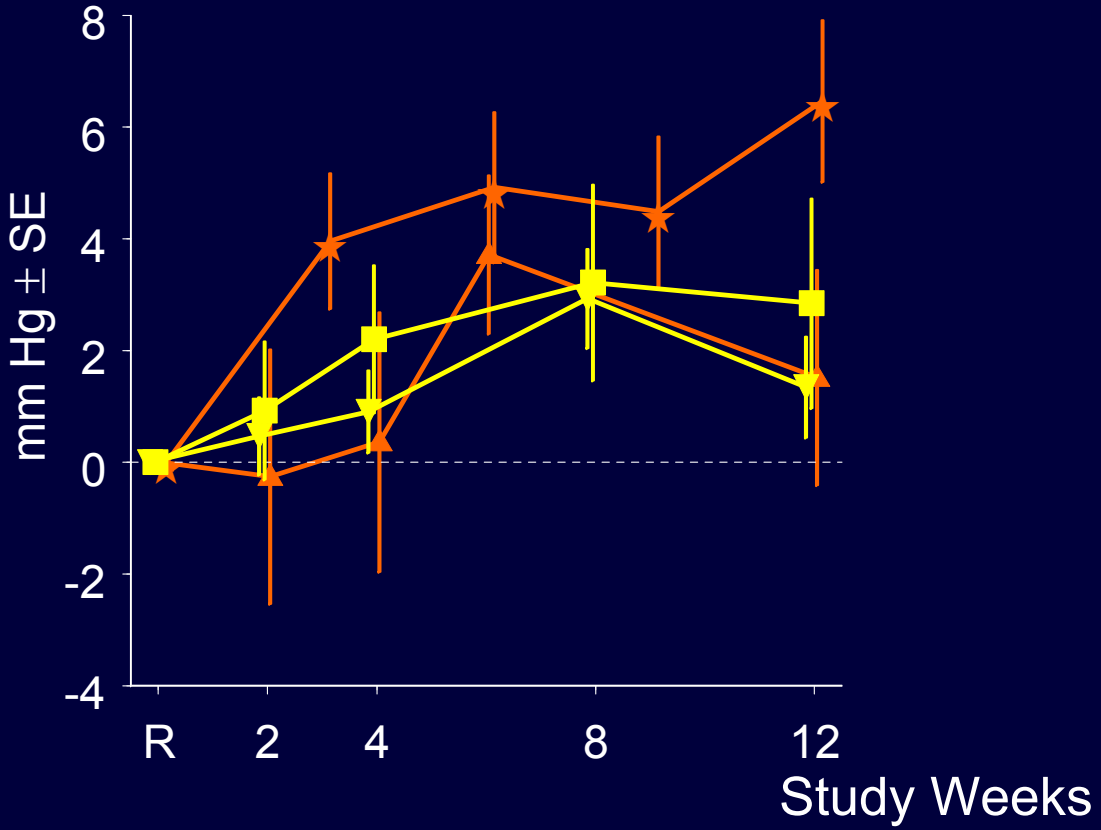
- Review of Efficacy
- Review of Safety
  - Thrombotic Cardiovascular (CV)
  - Upper Gastrointestinal (GI)
  - Renovascular
- Overview of Proposed Post-Approval Activities
- Summary

Renovascular Safety: OA Development Program and MEDAL Study

- OA Development Program (11 Studies)
  - Populations
    - Placebo-controlled (up to 12 weeks)
      - Placebo, etoricoxib, naproxen, ibuprofen, celecoxib
    - 6-Month: Etoricoxib, celecoxib
    - 1-Year: Etoricoxib, naproxen
  - Endpoints: BP Measures; Incidence of HTN, Edema, CHF AEs
- MEDAL Study
  - Endpoints: BP Measures; Patient Discontinuations for HTN, Edema AEs; Incidence of CHF (confirmed through adjudication)
    - MEDAL Study only collected AEs resulting in discontinuation or considered serious
- Analysis approach: All events through 14 days following last dose of therapy

OA Placebo-Controlled Population: Dose-dependent Increase in Systolic BP With Etoricoxib

Systolic BP: Mean Change from Baseline, Difference from Placebo (mm Hg)



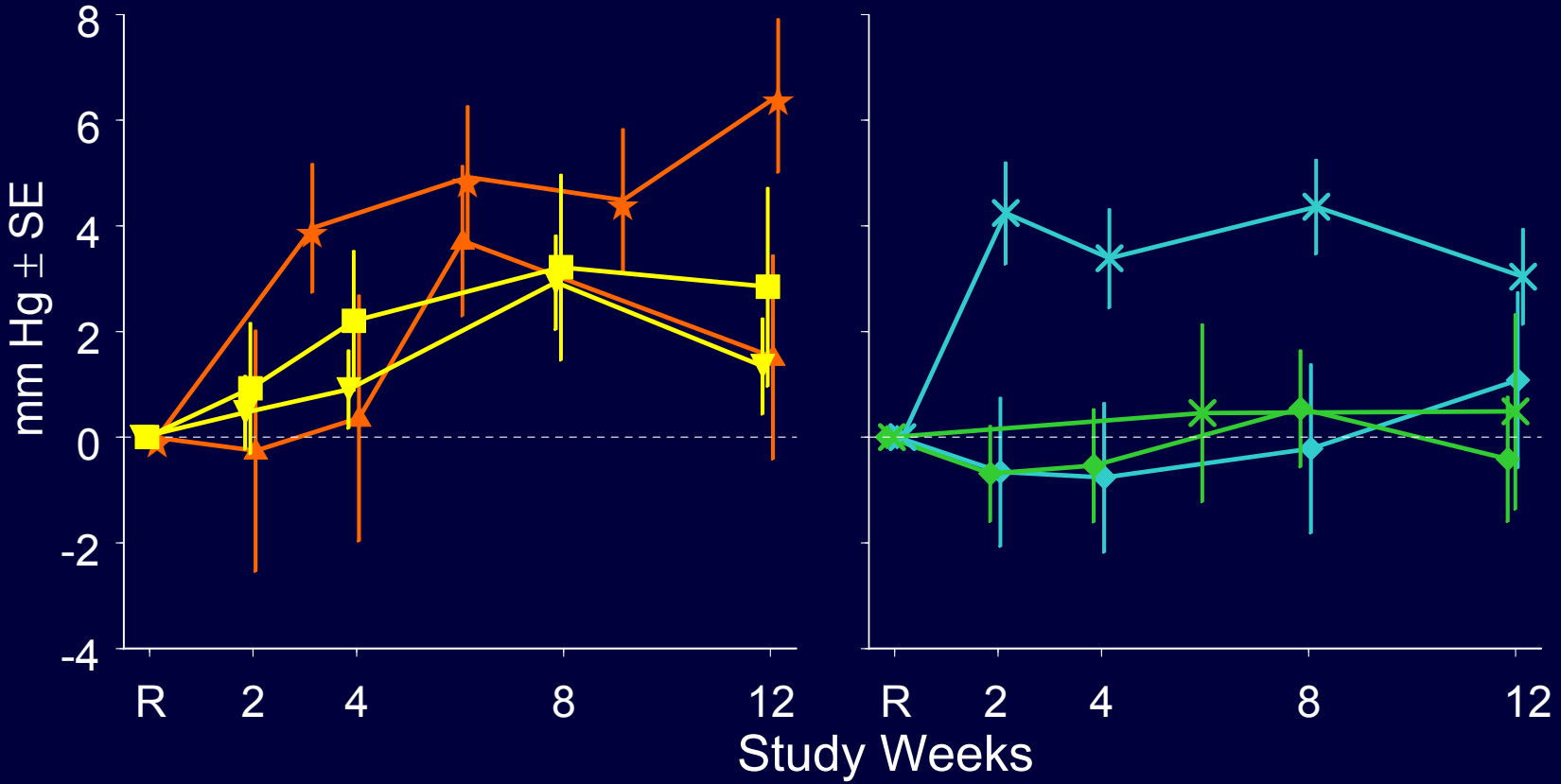
▼ Etoricoxib 30 mg ▲ Etoricoxib 90 mg

■ Etoricoxib 60 mg ★ Etoricoxib 120 mg

R = randomization, SE = standard error.

OA Placebo-Controlled Population: Systolic BP With Etoricoxib 30, 60 mg Between Effects of Naproxen, Ibuprofen

Systolic BP: Mean Change from Baseline, Difference from Placebo (mm Hg)



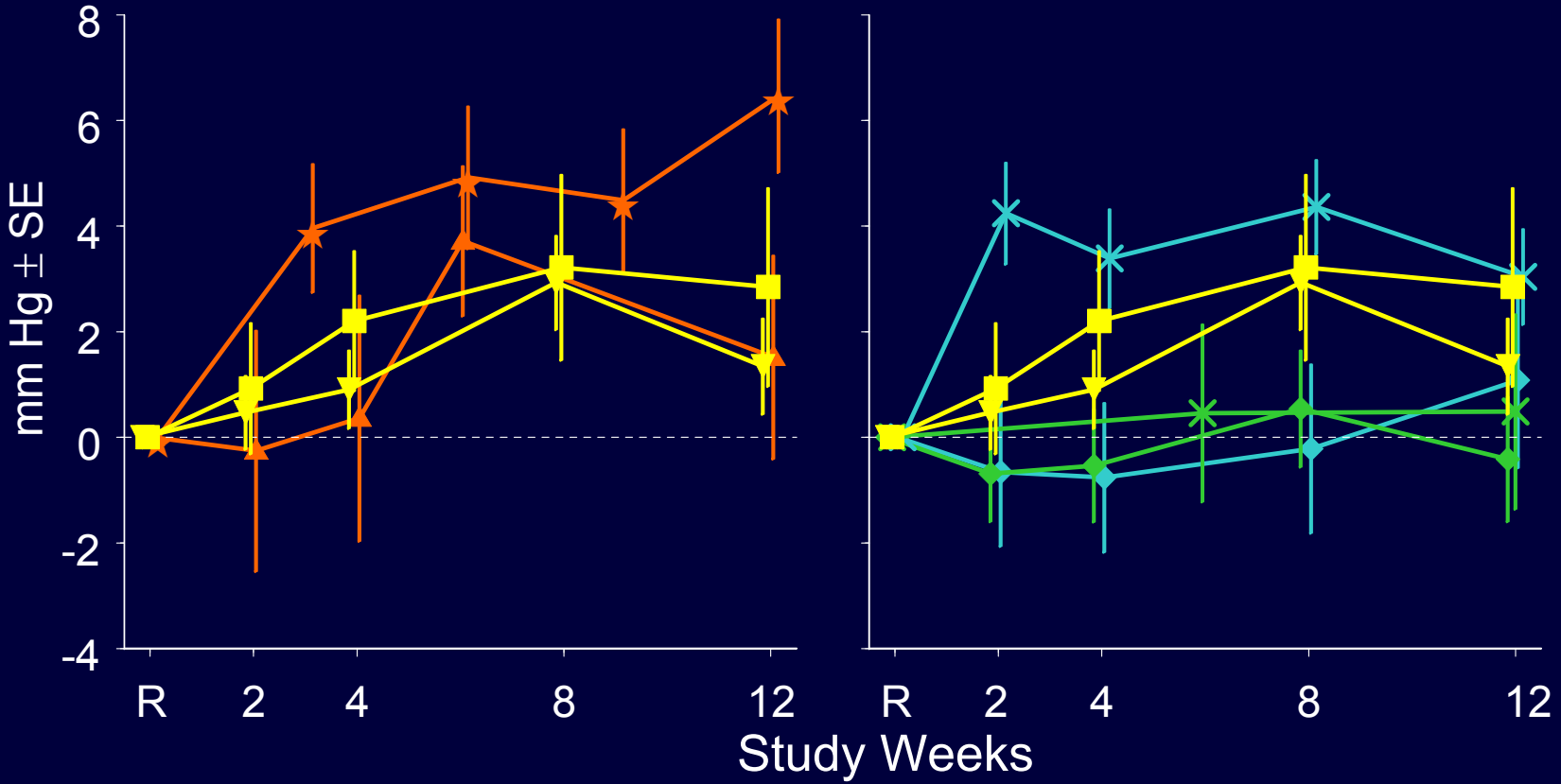
▼ Etoricoxib 30 mg ▲ Etoricoxib 90 mg ◆ Naproxen 1000 mg ◆ Celecoxib 200 mg

■ Etoricoxib 60 mg ★ Etoricoxib 120 mg ✖ Ibuprofen 2400 mg ✖ Celecoxib 400 mg

R = randomization, SE = standard error.

OA Placebo-Controlled Population: Systolic BP With Etoricoxib 30, 60 mg Between Effects of Naproxen, Ibuprofen

Systolic BP: Mean Change from Baseline, Difference from Placebo (mm Hg)

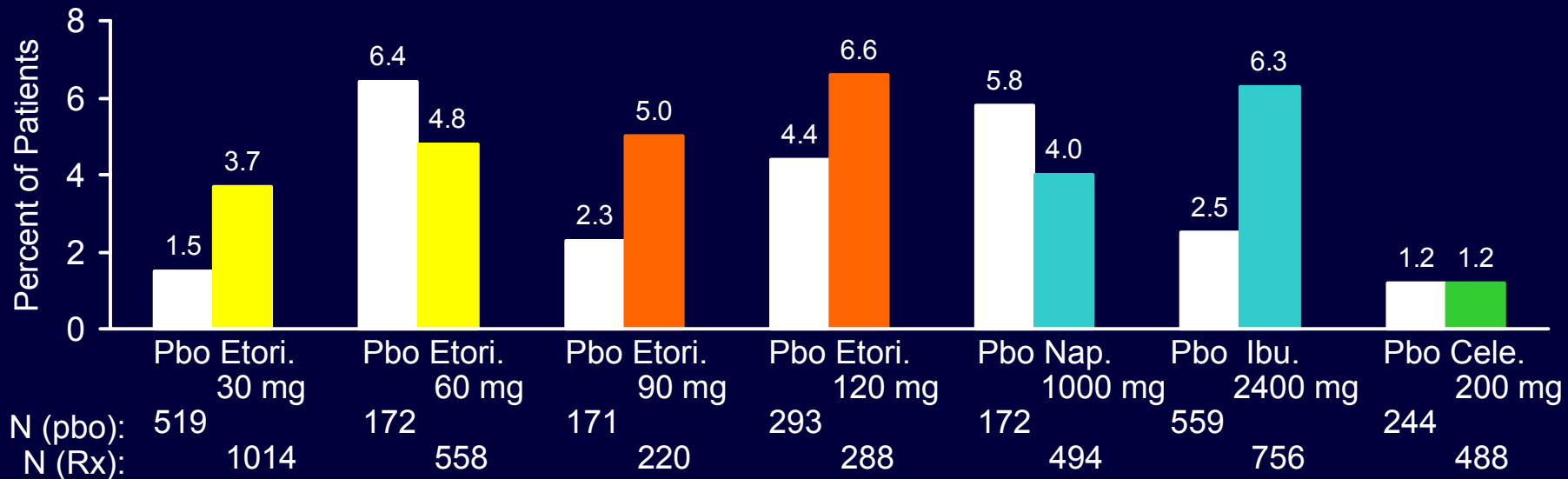


▼ Etoricoxib 30 mg ▲ Etoricoxib 90 mg ◆ Naproxen 1000 mg ◆ Celecoxib 200 mg

■ Etoricoxib 60 mg ★ Etoricoxib 120 mg ✖ Ibuprofen 2400 mg ✖ Celecoxib 400 mg

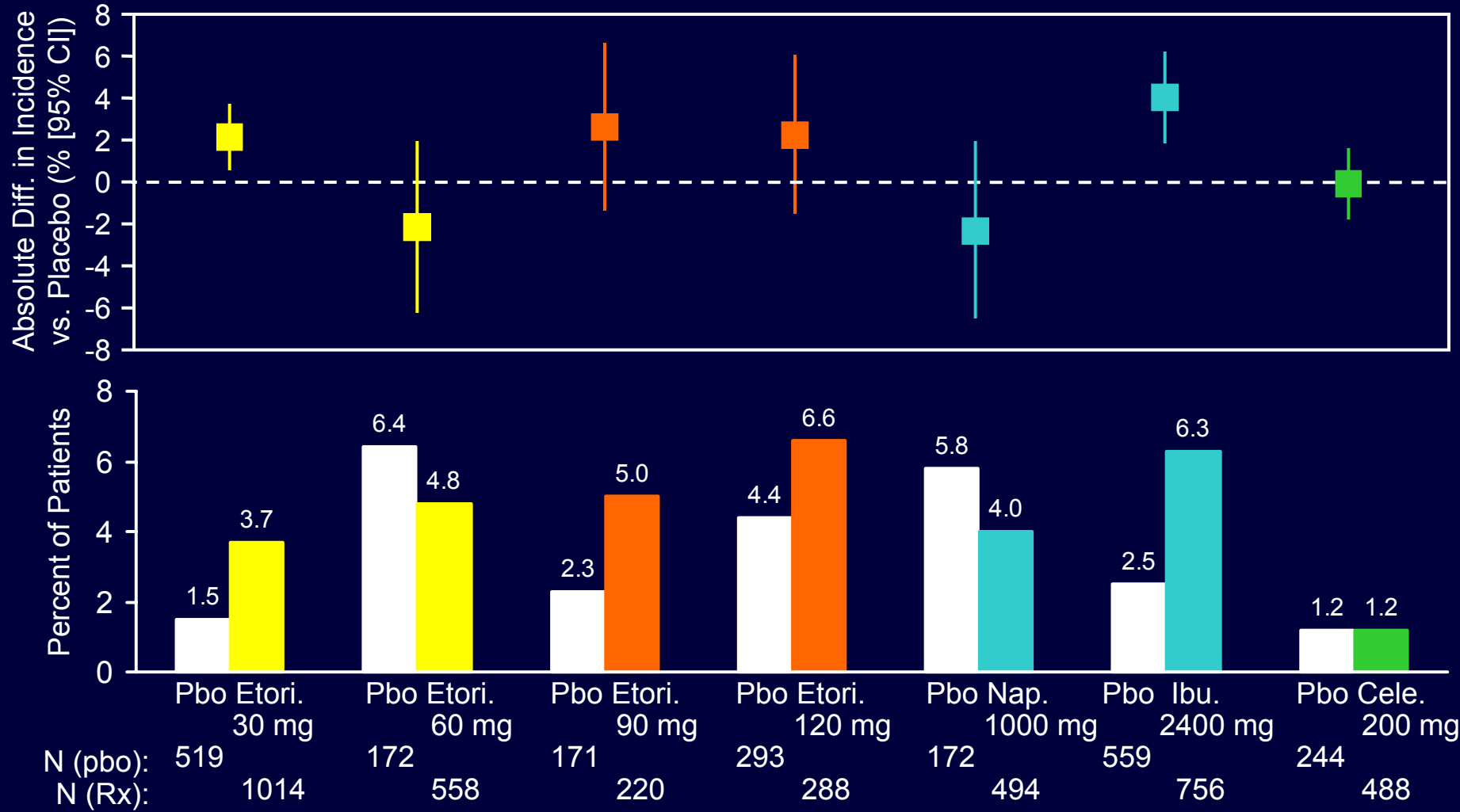
R = randomization, SE = standard error.

OA Development Program Placebo-Controlled Population: HTN AEs With Etoricoxib 30, 60 mg Between Incidence Observed With Naproxen 1000 mg, Ibuprofen 2400 mg



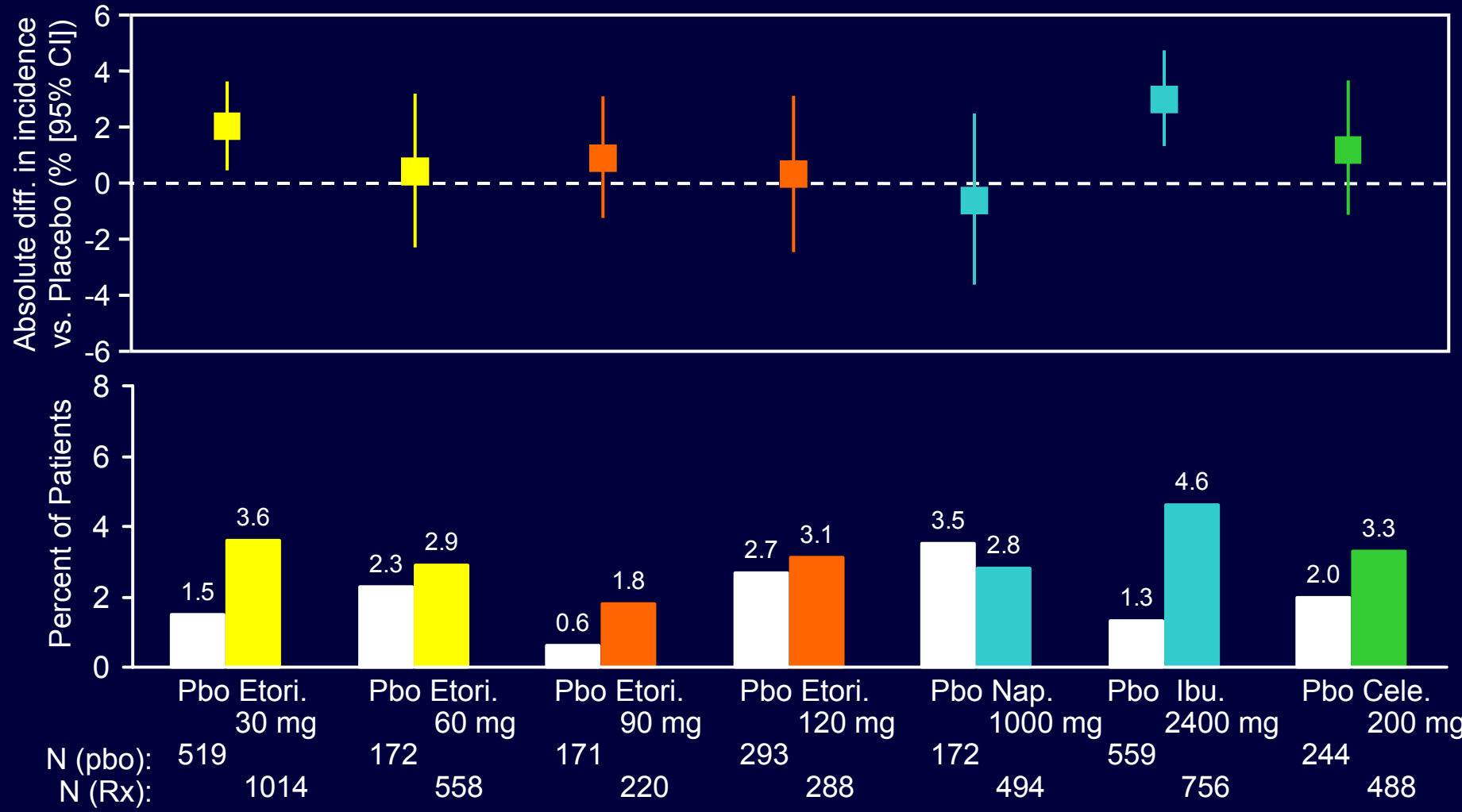
All events through 14 days following last dose of therapy.

OA Development Program Placebo-Controlled Population: HTN AEs With Etoricoxib 30, 60 mg Between Incidence Observed With Naproxen 1000 mg, Ibuprofen 2400 mg



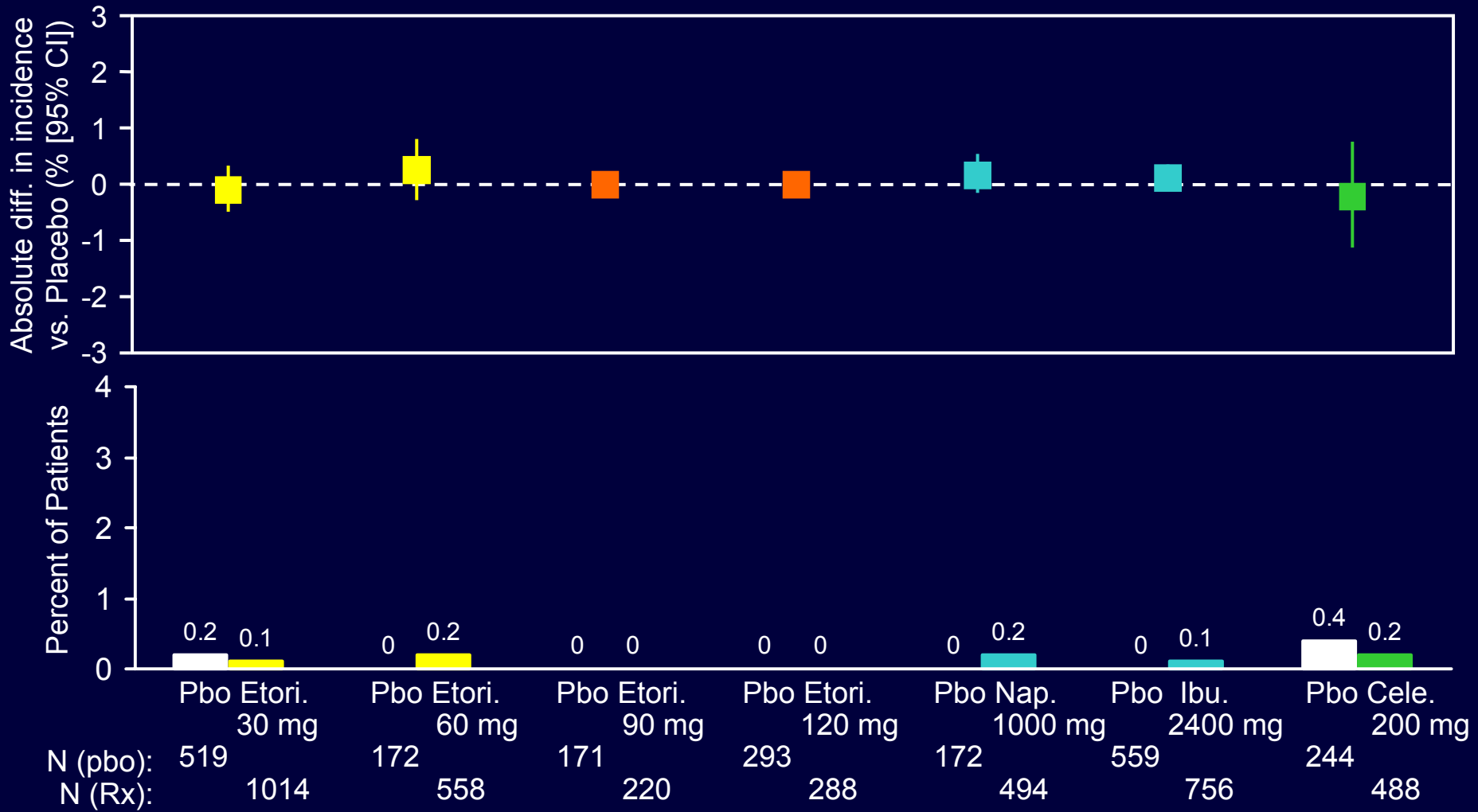
All events through 14 days following last dose of therapy.

OA Development Program Placebo-Controlled Population Edema AEs With Etoricoxib 30, 60 mg Similar to Naproxen 1000 mg, Ibuprofen 2400 mg



All events through 14 days following last dose of therapy.

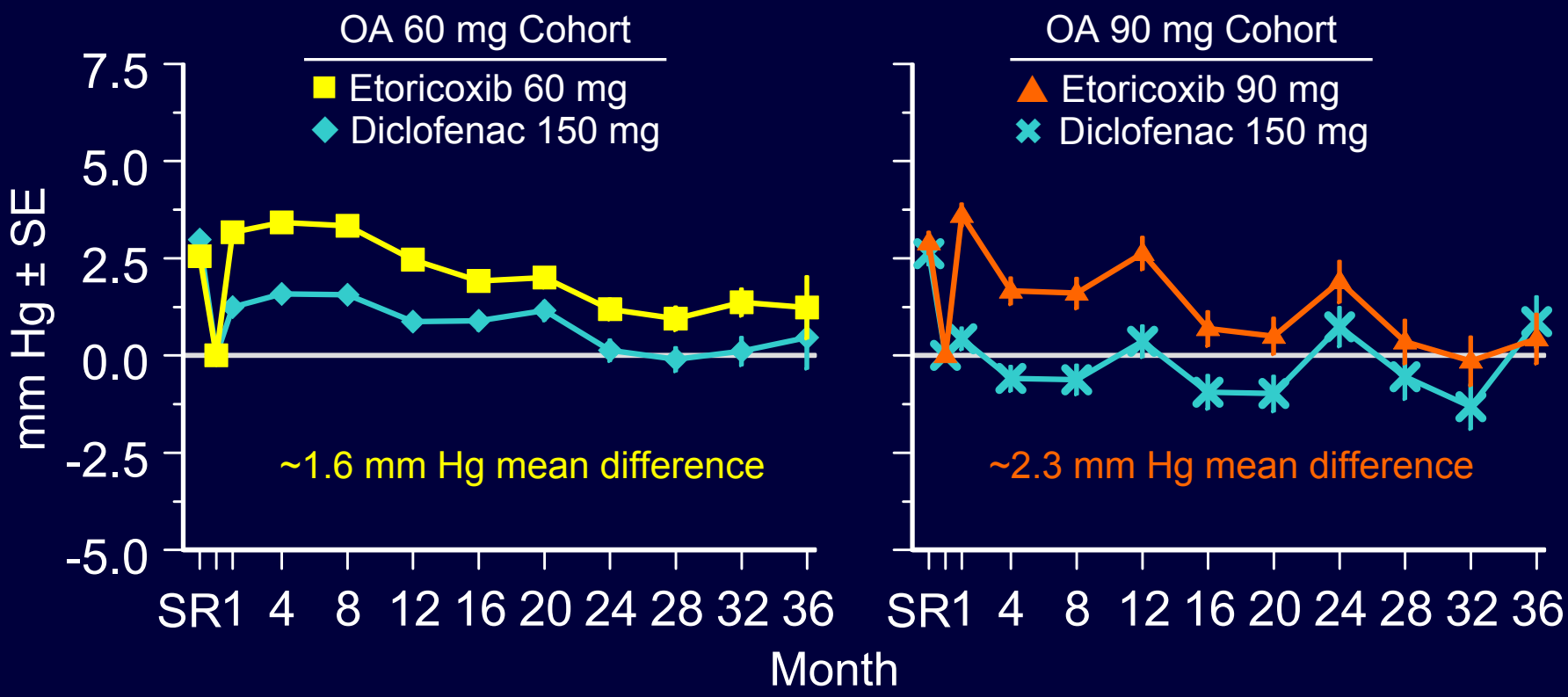
OA Development Program Placebo-Controlled Population CHF With Etoricoxib 30, 60 mg Similar to Naproxen 1000 mg, Ibuprofen 2400 mg



All events through 14 days following last dose of therapy.

MEDAL Study 60 mg OA Cohort: Mean Change in SBP ~1.6 mm Hg Higher With Etoricoxib 60 mg Than Diclofenac

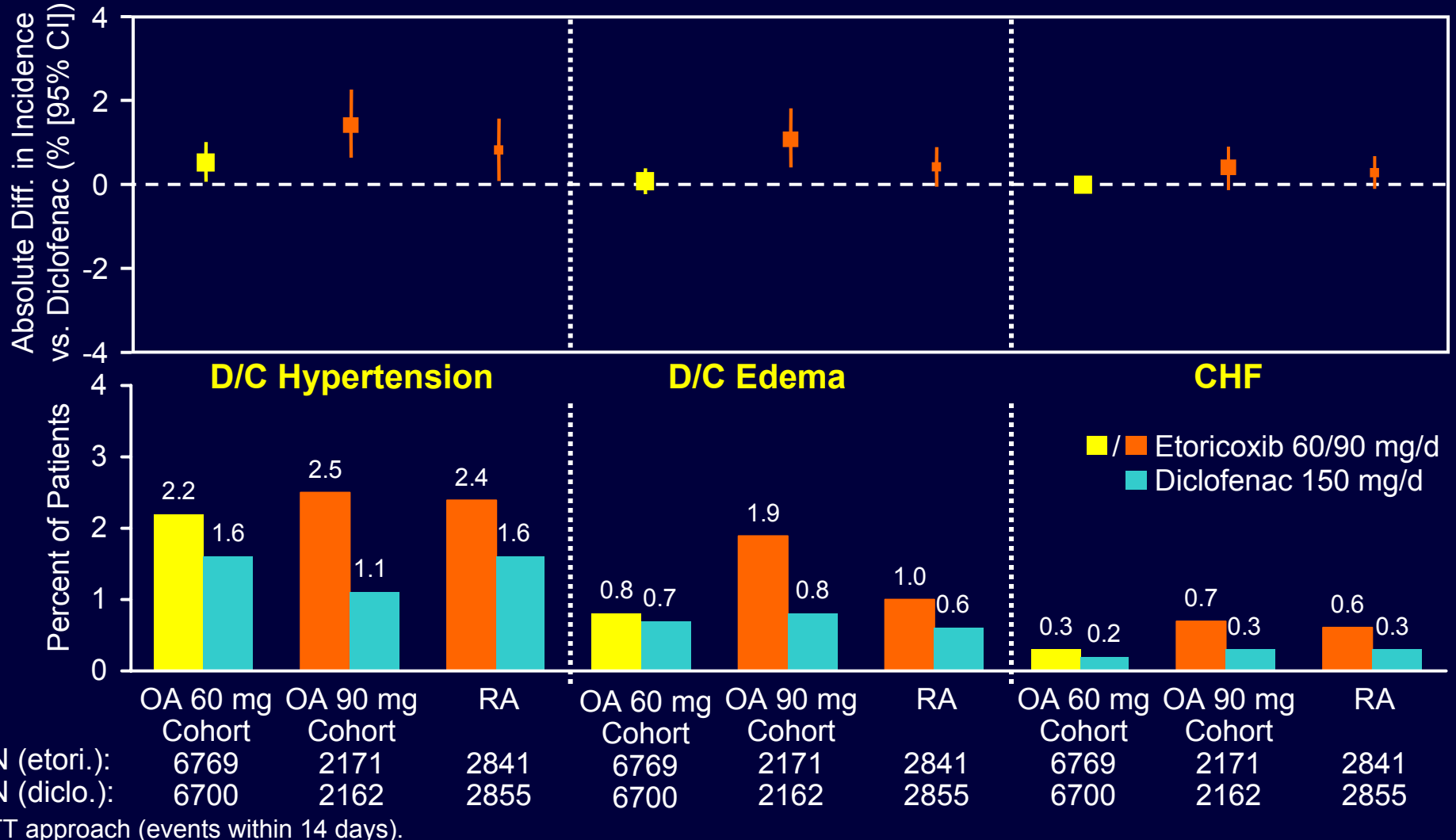
Systolic BP: Mean Change from Baseline (mm Hg)



N (Etoricoxib)	6769	5112	3472	437	2170	1408	1005	636
N (Diclofenac)	6699	4845	3314	444	2162	1320	927	626

S = screening, R = randomization, SE = standard error.

MEDAL Study OA 60 mg Cohort: Discontinuations Due to HTN Higher With Etoricoxib 60 mg; Edema, CHF Similar



ITT approach (events within 14 days).

Renovascular Safety Summary

- HTN: Effects for etoricoxib 30 and 60 mg between effects observed with traditional NSAIDs
- Edema: Incidence of AEs similar to traditional NSAIDs
- CHF: Incidence of AEs for etoricoxib 30 and 60 mg low, similar to traditional NSAIDs

Etoricoxib Presentation Overview

- Review of Efficacy
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Proposed Label Based on NSAID Class Template

- NSAID Boxed Warning
  - NSAID Cardiovascular Risk statements
    - NSAIDS may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk (see WARNINGS and CLINICAL TRIALS).
    - ARCOXIA is contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery (see CONTRAINDICATIONS and WARNINGS).
  - NSAID Gastrointestinal Risk statements
    - NSAIDS cause an increased risk of serious gastrointestinal adverse events, including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious gastrointestinal events (see WARNINGS).

Proposed Label Based on NSAID Class Template

- NSAID Warnings
  - NSAID warnings for Hypertension CHF, Edema
    - Hypertension
      - NSAIDs, including ARCOXIA, can lead to onset of new hypertension or worsening of pre-existing hypertension, either of which may contribute to the increased incidence of CV events
      - Blood pressure (BP) should be monitored closely during the initiation of NSAID treatment and throughout the course of therapy
    - Congestive Heart Failure and Edema
      - Fluid retention and edema have been observed in some patients taking NSAIDs, including ARCOXIA. ARCOXIA should be used with caution in patients with fluid retention or heart failure. (See ADVERSE REACTIONS.)
- Patient NSAID-class MedGuide distributed each time product dispensed

Proposed Post-Approval Activities

- Standard pharmacovigilance activities
  - Spontaneous adverse experience reporting
  - Periodic safety update reports
  - Initiate pregnancy registry
- Educate physicians and patients about NSAID (including etoricoxib) benefits and risks
  - Physician awareness of key attributes to be assessed by surveys
- Drug utilization studies to inform physician and patient education
  - Understand characteristics of patients prescribed etoricoxib
  - Understand product usage (dose, dose titration, duration)
- No plans for broadcast DTC television advertising at this time
  - Considered only after physicians aware of key attributes

Etoricoxib Presentation Overview

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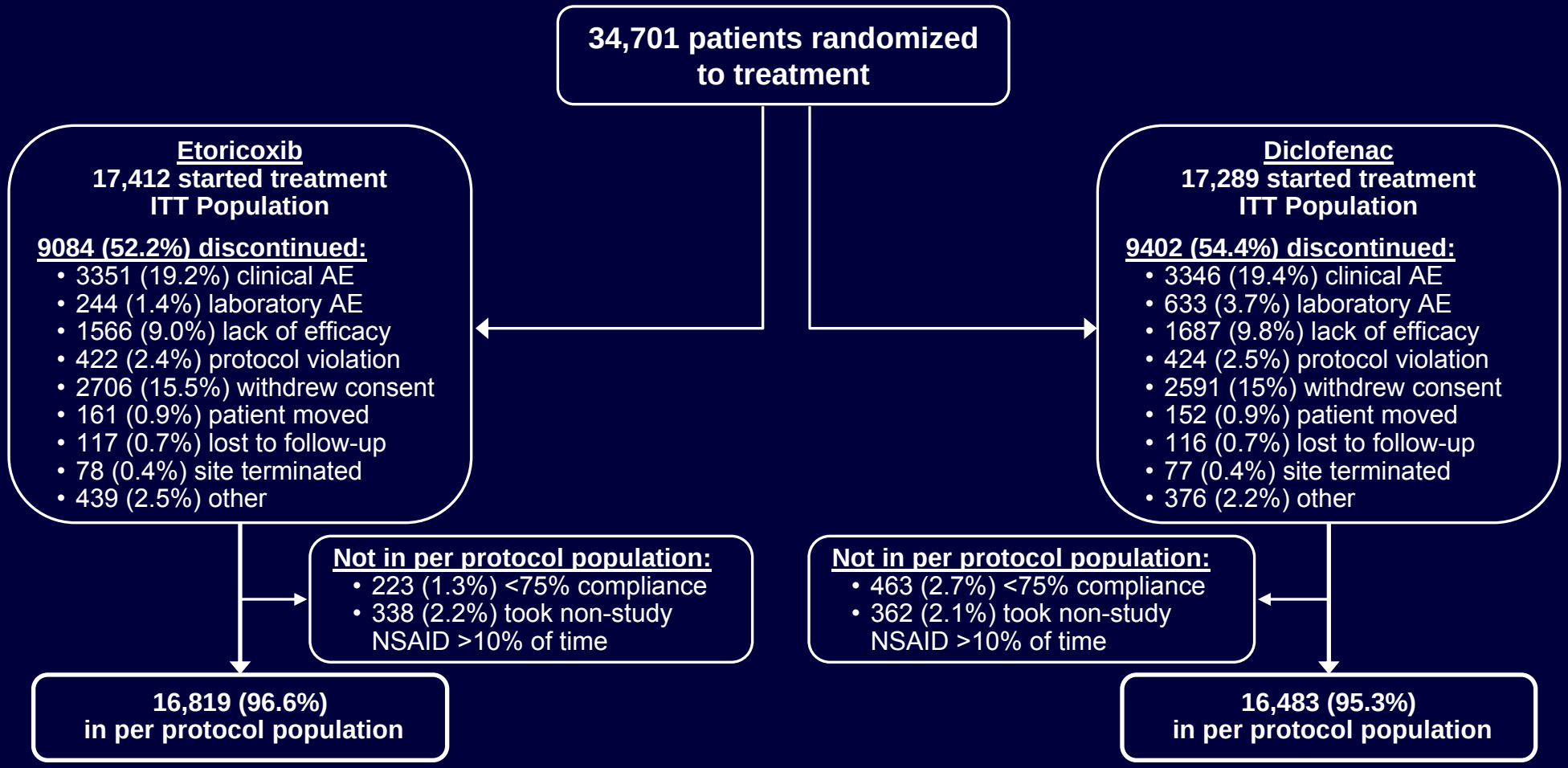
Etoricoxib: Favorable Benefit to Risk Profile in OA

- Robust efficacy with once daily dosing
  - 30 mg comparable to NSAIDs
  - 60 mg may provide additional benefit in some patients
    - Provides dosing flexibility based on individual patient needs
- Improved GI safety and tolerability compared to traditional NSAIDs
  - Ulcer reduction vs. diclofenac, maintained in presence of PPI
  - Improved GI tolerability, including fewer patient discontinuations for GI nuisance symptoms, decreased use of GI co-therapy
  - Favorable hepatic safety profile
- Effects on blood pressure dose-related, between effects observed with traditional NSAIDs
  - Can be monitored and treated
- Thrombotic CV safety profile consistent with prior randomized clinical trials of COX-2 selective vs. traditional NSAIDs

Etoricoxib: Valuable Treatment Option for OA

- Patients with osteoarthritis need additional treatment options
- Etoricoxib represents a valuable treatment that addresses this unmet need
- Well-established benefit to risk profile in patients for whom NSAID class therapy is indicated
  - Non-narcotic providing pain relief, improvement in physical functioning
  - Improved GI safety, tolerability in comparison to traditional NSAIDs, including in patients on a proton pump inhibitor
  - Thrombotic CV safety profile extensively characterized and consistent with non-naproxen NSAIDs

Pooled MEDAL Program Patient Disposition



Pooled MEDAL Program
Baseline Risk Factors for Confirmed UGI Events

Number of Risk Factors†	Etoricoxib		Diclofenac		Between Treatment Comparison	
	n/PYR	Rate‡	n/PYR	Rate‡	Relative Risk	95% CI
0	18/7956	0.23	28/7760	0.36	0.63	(0.35, 1.14)
1	50/11205	0.45	85/10762	0.79	0.57	(0.40, 0.80)
2	78/6277	1.24	107/5962	1.79	0.70	(0.52, 0.93)
3	28/913	3.07	23/838	2.74	1.12	(0.64, 1.94)
4	2/40	5.05	3/62	4.81	1.14	(0.19, 6.85)

† p-value for subgroup-by-treatment interaction non-significant. ITT (within 14 days).
‡ Rate = events per 100 patient-years.
The risk factors include age ≥65 years, baseline corticosteroid use, anti-platelet therapy use for at least 10% of time during study, and prior history of upper GI perforation, ulcer, or bleed.

Pooled MEDAL Program
Subgroup Analyses of Confirmed Overall UGI Events by Baseline use of Systemic Glucocorticoids and History of UGI Events

Subgroup	Etoricoxib		Diclofenac		Relative Risk (95% CI)
	n/PYR	Rate†	n/PYR	Rate†	
Baseline Use of Systemic Glucocorticoids‡					
No	127/21885	0.58	175/20948	0.84	0.69 (0.55, 0.87)
Yes	49/4506	1.09	71/4436	1.60	0.68 (0.48, 0.98)
History of UGI Events‡					
No	147/24678	0.60	214/23785	0.90	0.66 (0.53, 0.81)
Yes	29/1713	1.69	32/1599	2.00	0.85 (0.52, 1.41)

PYR = patient-years at risk; † Events per 100 patient-years.
‡ p-Value for treatment by subgroup interaction was not significant.

Pooled MEDAL Program
Confirmed Thrombotic Events
Subgroup Analysis of Demographics and CV Risk Factors (Per-protocol)

Subgroup		Etoricoxib n/PYR	Etoricoxib Rate†	Diclofenac n/PYR	Diclofenac Rate†	Relative Risk (95% CI)
Age	<65	134/15,761	0.85	135/15,261	0.88	0.96 (0.75, 1.21)
	≥65 to <75	123/7,567	1.63	120/7,309	1.64	0.99 (0.77, 1.27)
	≥75	63/2,508	2.51	68/2,196	3.10	0.81 (0.57, 1.14)
Gender	Female	191/19,190	1.00	176/18,433	0.95	1.04 (0.85, 1.28)
	Male	129/6,646	1.94	147/6,333	2.32	0.83 (0.66, 1.05)
Baseline Low Dose Aspirin Use	No	173/17,047	1.01	166/16,391	1.01	1.00 (0.81, 1.24)
	Yes	147/8,789	1.67	157/8,375	1.87	0.89 (0.71, 1.12)
History of Diabetes	No	266/23,285	1.14	279/22,252	1.25	0.91 (0.77, 1.07)
	Yes	54/2,552	2.12	44/2,514	1.75	1.21 (0.81, 1.80)
History of Dyslipidemia	No	196/18,543	1.06	206/17,863	1.15	0.92 (0.75, 1.11)
	Yes	124/7,293	1.70	117/6,903	1.69	1.00 (0.78, 1.29)
History of Hypertension	No	120/14,139	0.85	128/13,177	0.97	0.87 (0.68, 1.12)
	Yes	200/11,697	1.71	195/11,589	1.68	1.01 (0.83, 1.23)
History of Symptomatic ASCVD	No	235/23,113	1.02	234/22,092	1.06	0.96 (0.80, 1.15)
	Yes	85/2,723	3.12	89/2,674	3.33	0.94 (0.70, 1.26)
Current Cigarette User	No	258/22,809	1.13	266/21,766	1.22	0.92 (0.78, 1.09)
	Yes	62/3,028	2.05	57/3,000	1.90	1.09 (0.76, 1.56)

PYR = patient-years at risk; † Events per 100 patient-years.

Pooled MEDAL Program
CV Baseline Patient Characteristics

Baseline Cardiovascular Risk	Etoricoxib N=17,412 %	Diclofenac N=17,289 %
Hx of Diabetes	10.4	10.7
Hx of Dyslipidemia	29.3	29.1
History of HTN	46.6	47.6
Cigarette User (Current)	11.7	11.8
Family Hx of CV Disease	17.8	17.9
History of Symptomatic ASCVD	11.6	11.6
Increased Risk (Hx of Symptomatic ASCVD or ≥2 CV Factors)	37.8	38.4
Baseline Low-Dose Aspirin Users†	34.6	34.6

† Baseline low dose aspirin users were defined as patients using aspirin (≤325 mg) at trial start date or +1 day; or patients using aspirin (≤1300 mg) for 50% of time during one month (range from -30 to -1) prior to trial start date.

MEDAL Program
Major Exclusion Criteria

- Morbid obesity
- Uncontrolled hypertension (sitting diastolic >95 mm, systolic >165 mm Hg)
- Severe CHF (NYHA Class III or IV)
- Cerebrovascular event, CABG, angioplasty <6 months prior to enrollment, or unstable angina
- Impaired renal function (CCr <30 mL/min or sCr >2.0 mg/dL)
- Active hepatic disease
- Severe (class IV) RA
- Requiring warfarin, heparin, high-dose ASA, ticlopidine or clopidogrel plus low-dose ASA, non-study NSAID or COX-2 selective inhibitor
- GI malabsorption, inflammatory bowel disease, or positive fecal occult blood test
- Bleeding diathesis

CCr = creatinine clearance; sCr = serum creatinine.

Pooled MEDAL Program
Confirmed APTC Endpoint by Class of Terms
Per-protocol Approach

	Etoricoxib (N=16,819)		Diclofenac (N=16,483)	
	n	Rate†	n	Rate†
Total Patients With Endpoint	216	0.84	216	0.87
Cardiac Events	142	0.55	145	0.58
Non-fatal myocardial infarction	105	0.41	105	0.42
Fatal myocardial infarction	6	0.02	17	0.07
Sudden cardiac death	29	0.11	23	0.09
Resuscitated cardiac arrest	2	0.01	1	0.00
Cerebrovascular Events	59	0.23	57	0.23
Non-fatal ischemic cerebrovascular stroke	53	0.21	55	0.22
Fatal ischemic cerebrovascular stroke	6	0.02	2	0.01
Peripheral Vascular Events	2	0.01	1	0.00
Fatal pulmonary embolism	1	0.00	0	0.00
Fatal peripheral arterial thrombosis	1	0.00	1	0.00
Other Events	15	0.06	16	0.06
Fatal GI hemorrhage	1	0.00	2	0.01
Fatal hemorrhagic cerebrovascular stroke	5	0.02	4	0.02
Fatal vascular rupture	2	0.01	0	0.00
Non-fatal hemorrhagic cerebrovascular stroke	7	0.03	10	0.04

† Events per 100 patient-years.

CHF Adjudication

- CHF adjudication implemented in December 2005 upon recommendation by the MEDAL Program Data and Safety Monitoring Board (DSMB) to adjudicate cases resulting in hospitalization and was endorsed by the MEDAL Program Steering Committee
- Merck performed continuous surveillance for eligible prespecified CHF terms in SAE reports† occurring on therapy or within 28 days of discontinuation of study therapy in all MEDAL program studies (EDGE, EDGE II and MEDAL)
- Investigator requested source documents from hospital or healthcare providers for all potential events
- All CHF endpoint packages reviewed by the independent, blinded cardiology adjudication committee
  - Prespecified criteria for confirmation and classification
- Committee members reviewed cases independently then final joint adjudication by consensus

† All hospitalizations or emergency department visits for CHF.

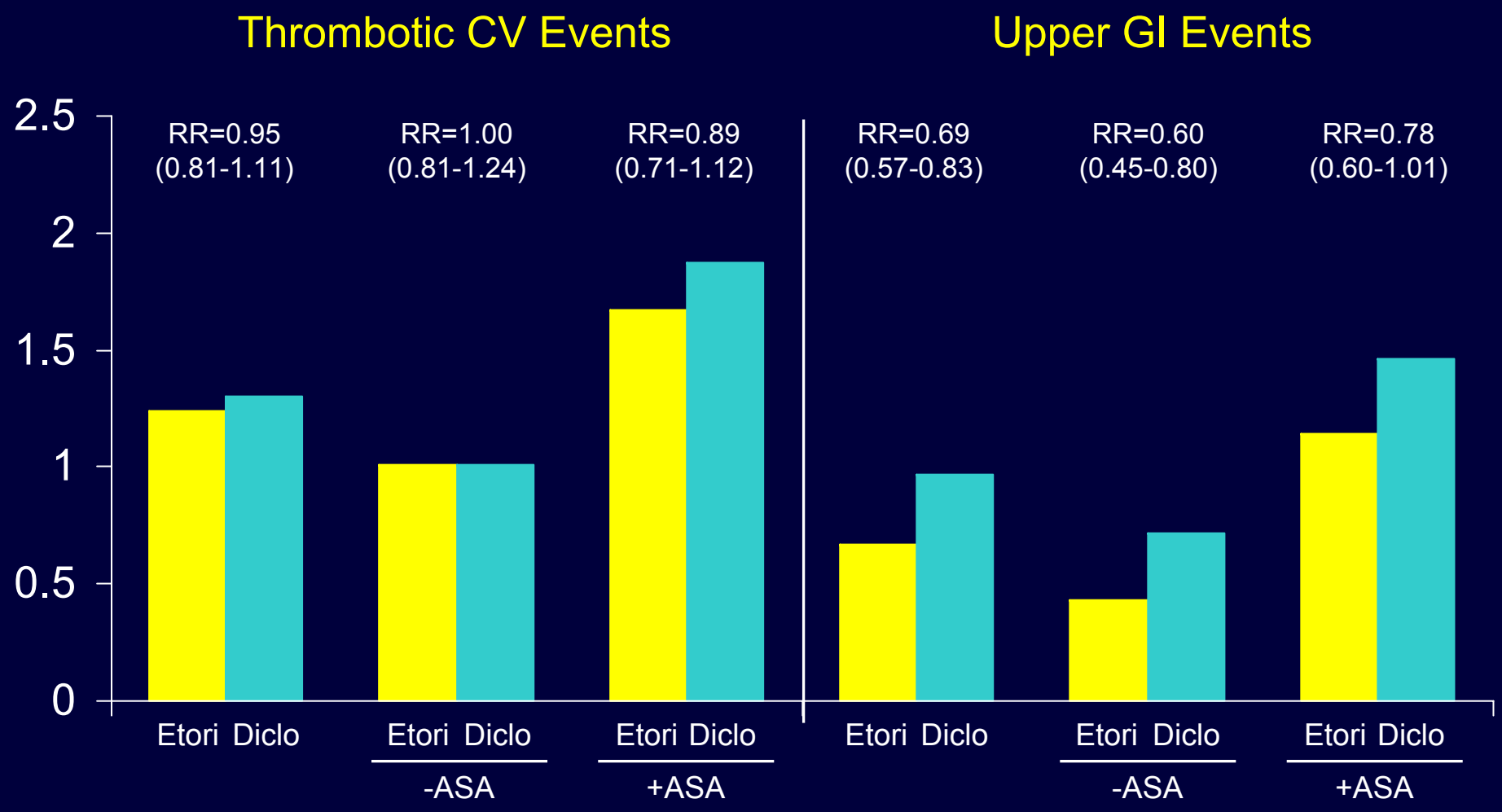
Adjudication of CHF-Related Adverse Experiences

- All potential cases of heart failure referred to independent, blinded committee of experts
  - Eligible cases included those resulting in hospitalization or an emergency room visit
- Diagnosis based on broadly inclusive, pre-specified list of terms, retrospective data review and predefined criteria for:
  - Symptoms
  - Signs of CHF, laboratory data or imaging considered supportive evidence
  - Treatment

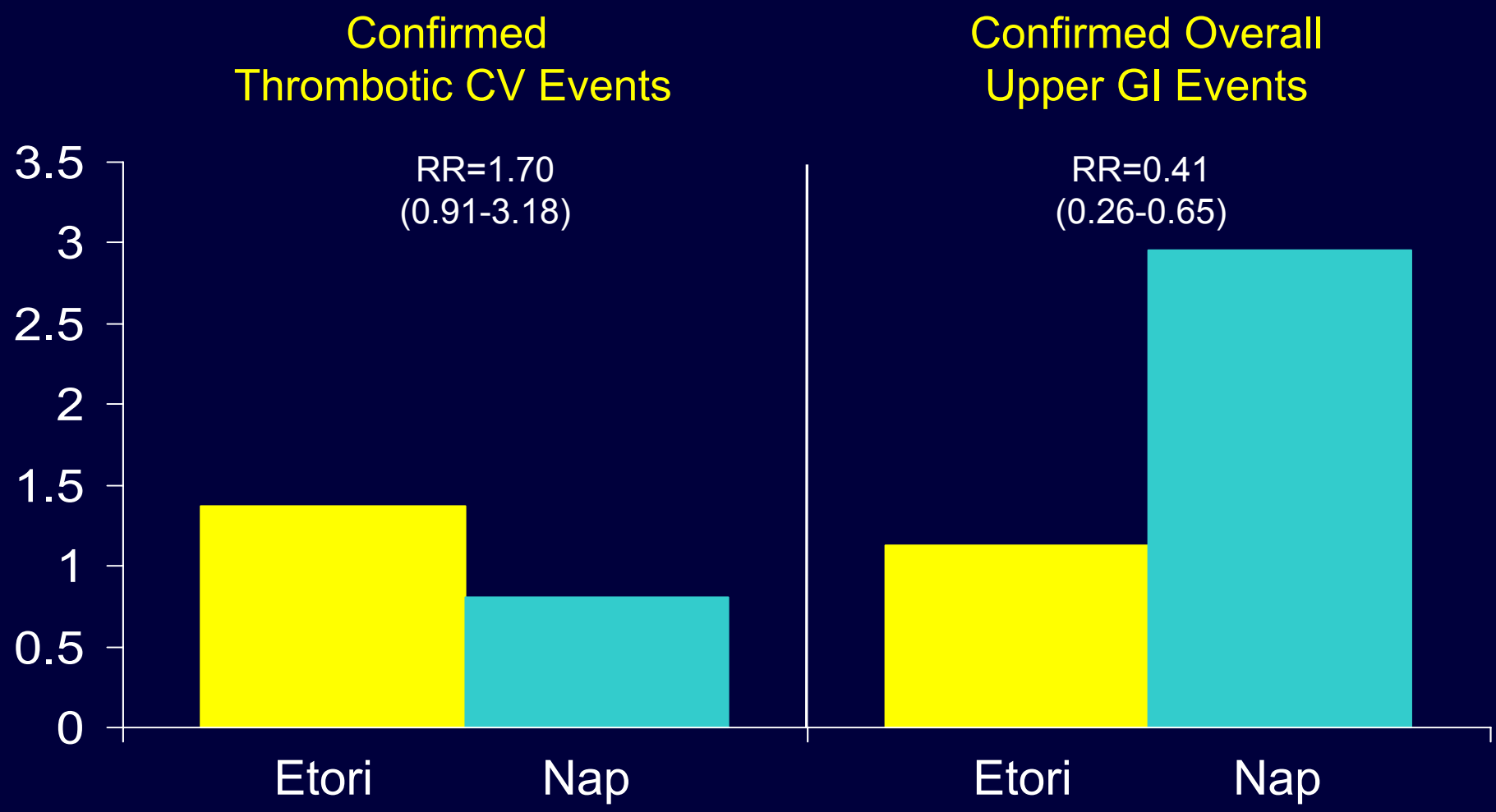
Criteria for Confirmed CHF-Related AEs

- Diagnosis of heart failure relies on clinical judgment and requires:
  - Hospital admission or Presentation to the Emergency Department
  - Symptoms consistent with heart failure
  - Heart Failure treatment which may include:
    - Augmentation of oral medications (significant increase in dose or frequency of administration)
    - New administration of intravenous heart failure therapy (inotropes, diuretics, or vasodilators)
  - Response to therapy is evaluated using the following criteria:
    - Resolution of pulmonary edema
    - Decrease in wedge pressure
    - Significant diuresis
- Diagnosis may be supported by signs of heart failure or imaging and/or laboratory evidence of cardiac dysfunction and/or structural abnormality

MEDAL Program
Comparative Assessment of Thrombotic and Upper GI Events Overall and by Aspirin Use



Etoricoxib Development Program
Naproxen Controlled Data Set
Confirmed Thrombotic CV and Overall Upper GI Events



GPRD Study of Etoricoxib Users Design

- Descriptive observational study to evaluate / estimate
  - Characteristics of patients newly prescribed etoricoxib
  - Patterns of etoricoxib prescribing by GPs in UK
  - Absolute incidence rate of AEs among new users
- Study population / period
  - New etoricoxib users April 2002 through June 2006
    - Four cohorts defined by date of first etoricoxib prescription
      - 1 - Apr 1, 2002 to Sep 30, 2003
      - 2 - Oct 1, 2003 to Sep 30, 2004
      - 3 - Oct 1, 2004 to Feb 17, 2005
      - 4 - Feb 18, 2005 to Jun 30, 2006

GPRD Study of Etoricoxib Users
Number of New Users, Demographics, Indications

- 21,320 new users overall
- Demographics (constant over time)
  - 60% female
  - Mean and median age 60 years
  - 40% ≥65 years
- Indication
  - 34-40% OA
  - 4-5% RA
  - 8-13% gout
  - 5% unspecified arthritis
  - 36-41% none of the above in patient record

GPRD Study of Etoricoxib Users
Incidence of GI Events During Initial Course of Therapy
Patients Without Prior Medical History, Initial Dose 60 mg

Number of Patients (rate/1000 PYR*), by Time Period, 60 mg Dose

	Time Period†			
Event	1	2	3	4
PUB	7 (6.75)	9 (8.33)	3 (6.16)	0 (0.0)

* PYR = patient-years.

† Time periods:
1 = Apr 1, 2002 – Sep 30, 2003. 2 = Oct 1, 2003 – Sep 30, 2004.
3 = Oct 1, 2004 – Feb 17, 2005. 4 = Feb 18, 2005 – June 30, 2005.

GPRD Study of Etoricoxib Users
GI Baseline Medical History, All Indications

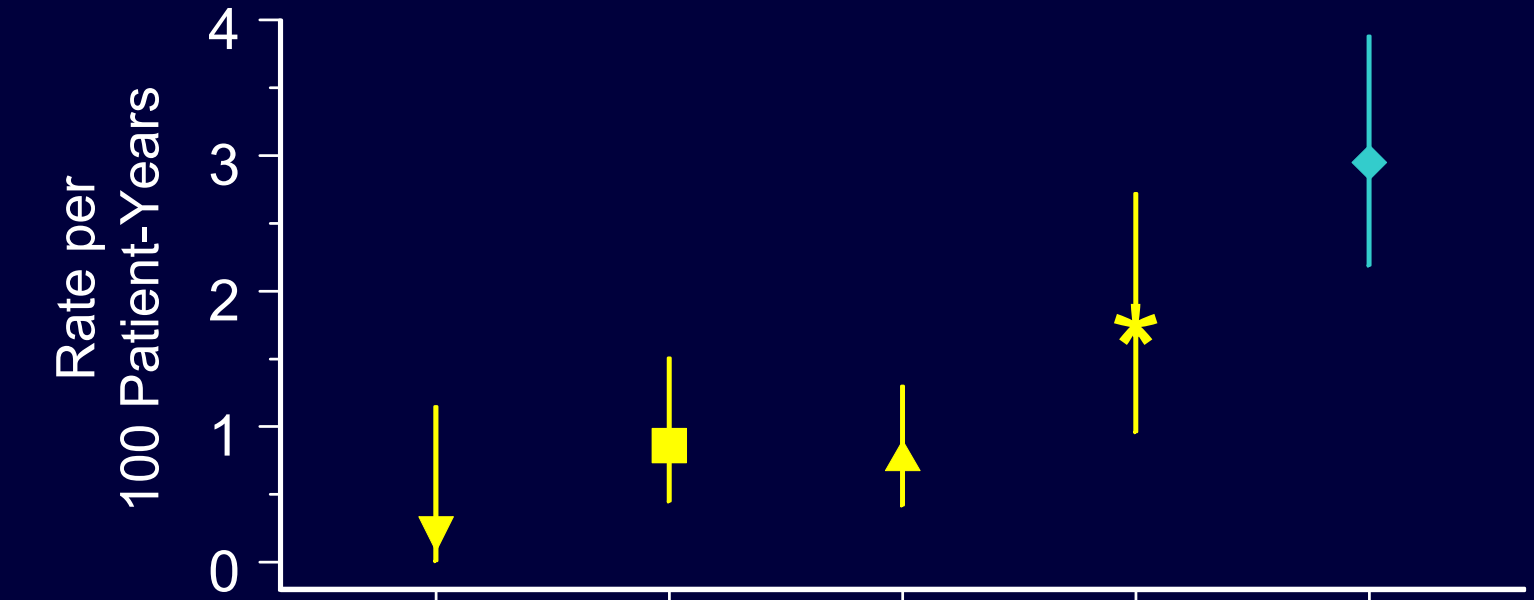
Percent of Patients, by Time Period

Baseline Condition	Time Period* 1 (N=7525)	2 (N=9414)	3 (N=3346)	4 (N=1035)
PUB	8.92	8.40	8.49	7.92

* Time periods:
1 = Apr 1, 2002 – Sep 30, 2003. 2 = Oct 1, 2003 – Sep 30, 2004.
3 = Oct 1, 2004 – Feb 17, 2005. 4 = Feb 18, 2005 – June 30, 2005.

Etoricoxib Development Program
Rates of Confirmed Overall Upper GI Events by Dose Over the Entire Treatment Period

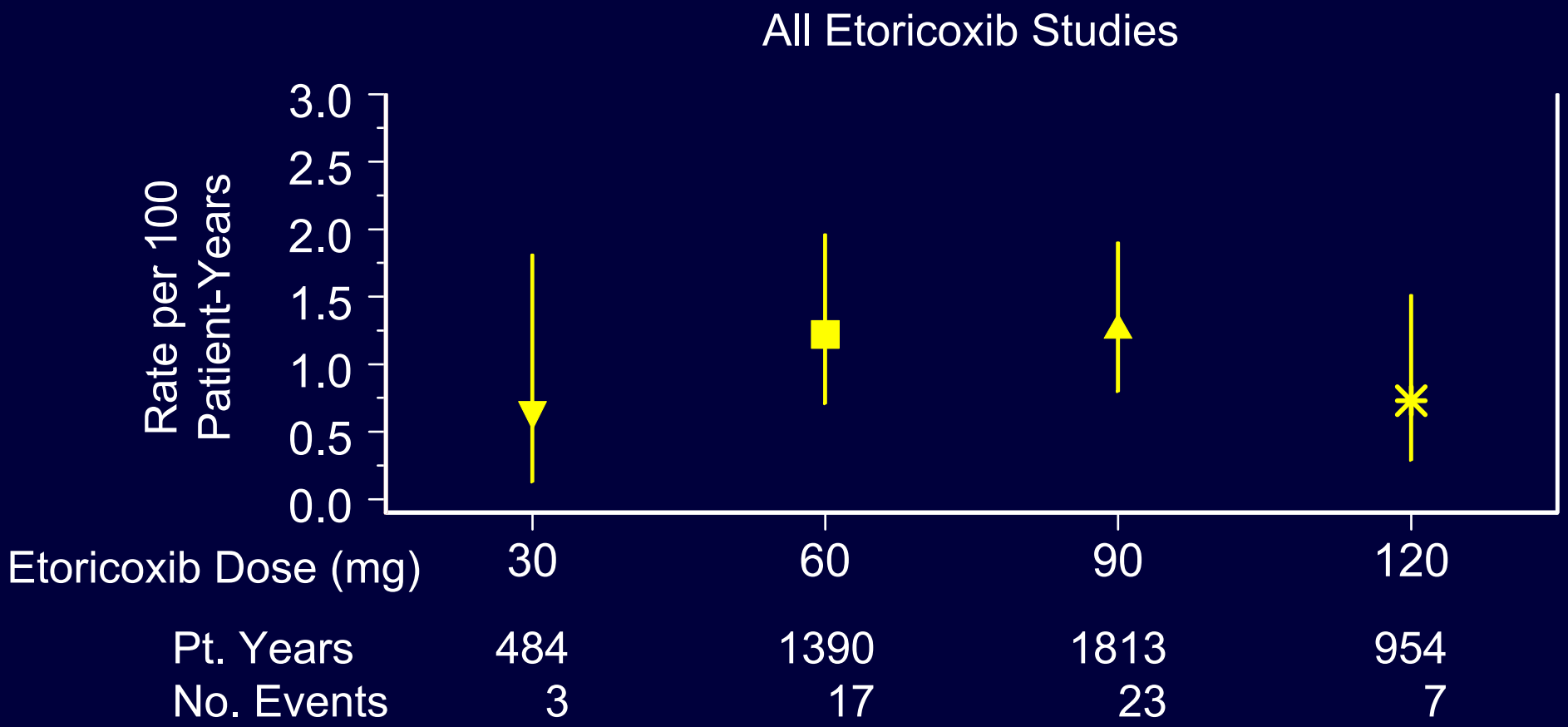
Rates per 100 Patient-Years and 95% CI



Dose (mg)	Etori 30	Etori 60	Etori 90	Etori 120	Naproxen 1000
Pt. Years	484	1390	1813	954	1730
Cases	1	12	14	16	51

Etoricoxib Development Program
Confirmed Thrombotic Events
Rate by Etoricoxib Dose

Rates per 100 Patient-Years With 95% CI



Etoricoxib Development Program
Summary of Mortality
mITT Approach (Events Within 14 days)

	Placebo PYR=450		Etoricoxib PYR=4642		Non-Naproxen NSAIDs PYR=914		Naproxen PYR=1731	
	n	Rate (95% CI)‡	n	Rate (95% CI)‡	n	Rate (95% CI)‡	n	Rate (95% CI)‡
Overall Mortality	1	0.22 (0.01, 1.24)	20	0.43 (0.26, 0.67)	3	0.33 (0.07, 0.96)	5	0.29 (0.09, 0.67)
CV Deaths	0	0.00 (0.00, 0.82)	10	0.22 (0.10, 0.40)	2	0.22 (0.03, 0.79)	3	0.17 (0.04, 0.51)
Thrombotic CV Deaths	0	0.00 (0.00, 0.82)	9	0.19 (0.09, 0.37)	2	0.22 (0.03, 0.79)	2	0.12 (0.01, 0.42)
Non-CV Deaths	1	0.22 (0.01, 1.24)	10	0.22 (0.10, 0.40)	1	0.11 (0.00, 0.61)	2	0.12 (0.01, 0.42)

‡ Rate = Events per 100 patient-years.

MEDAL Study
Baseline Medication Use

Prior Use of Specific Prior Medications	OA 60 mg Cohort		OA 90 mg Cohort		Rheumatoid Arthritis	
	Etori 60 mg N=6769 %	Diclo 150 mg N=6700 %	Etori 90 mg N=2171 %	Diclo 150 mg N=2162 %	Etori 90 mg N=2841 %	Diclo 150 mg N=2855 %
MTX (RA patients)	--	--	--	--	54.2	54.8
DMARDS (RA patients)	--	--	--	--	39.4	38.8
Statins	15.9	16.1	27.2	27.6	11.3	10.6
ACE Inhibitors	19.0	18.8	20.0	20.4	17.2	16.8
Etoricoxib	0.7	0.7	0.0	0.1	0.9	0.9
Diclofenac Sodium	19.6	19.4	4.0	4.8	18.9	20.1
Coxibs	21.3	21.5	40.0	43.5	29.2	29.6
NSAIDS	76.9	77.4	87.1	89.4	88.0	88.3
Antiplatelet	38.0	37.6	53.2	54.6	32.4	33.6

Etoricoxib Development and MEDAL Programs Summary of GI Tolerability

Subgroup	Treatment	N	n/PYR	Rate†	Relative Risk (95% CI)
Development Program					
New Use of Concomitant GPAs	Etoricoxib	3635	397/3941	10.07	0.75 (0.64, 0.87)
	NSAIDs	2497	319/2092	15.24	
Discontinuation Due to NSAID-Type AEs	Etoricoxib	3635	75/4179	1.79	0.62 (0.45, 0.86)
	NSAIDs	2497	76/2264	3.36	
MEDAL Program					
Discontinuation Due to GI Clinical AEs	Etoricoxib	17412	1023/26,082	3.92	0.69 (0.64, 0.75)
	Diclofenac	17289	1428/25,079	5.69	
Discontinuation Due to Hepatic AEs	Etoricoxib	17412	57/26,082	0.22	0.12 (0.09, 0.16)
	Diclofenac	17289	461/25,079	1.84	

† Number of events per 100 patient-years; PYR = Patient-years of risk; CI = confidence interval.

Osteoarthritis: Disease Burden and Unmet Patient Needs

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Osteoarthritis: Disease Burden

- Most common musculoskeletal disease in USA
- Prevalence of symptomatic osteoarthritis
  - 12.1% of general population
  - >21,000,000 patients[1]
  - Projected increase with aging population
- Decrease in function and Quality of Life[2]

1. Lawrence et al. Estimates of the prevalence of arthritis and selected musculoskeletal disorders in the United States. *Arthritis and Rheumatism* 1998; 41:778-799.
2. Spranger et al. Which chronic conditions are associated with better or poorer quality of life. *Journal of Clinical Epidemiology*. 2000; 53:895-907.

Treatments Options
ACR Osteoarthritis Guidelines[1]

- Non pharmacologic – Large range of options each with small-moderate benefit
- Pharmacologic
  - Acetaminophen
  - Nonselective NSAID with or without misoprostol or a proton pump inhibitor
  - COX-2 selective inhibitor
  - Nonacetylated salicylates
  - Pure analgesics – tramadol, opioids
  - Intraarticular injections
  - Topical Agents – Capsaicin, Methylsalicylate
- No universally effective pharmacologic therapy
- Benefit risk ratio varies with each option

1. American College of Rheumatology subcommittee on osteoarthritis guidelines. Recommendations for the Medical Management of Osteoarthritis of the Hip and Knee. Arthritis and Rheumatism 2000; 43: 1905-1915.

Considerations for Choice of Pharmacologic Treatment

- Evidence-based Medicine: Individualized selection of treatments based on benefit/risk assessment by physician and patient.
- NSAIDs and COX-2 selective inhibitors have greater efficacy, and toxicity, than acetaminophen[1,2]
- Only 27% - 42% of patients at risk of upper GI complications receive gastroprotective therapy[3,4]
- Failed adherence to gastroprotective therapy is a serious problem in preventing GI complications.

1. Pincus T et al. A randomized, double-blind, crossover clinical trial of diclofenac plus misoprostol versus acetaminophen in patients with osteoarthritis of the hip or knee. *Arthritis Rheum*. 2001; 44:1587-98.
2. Towheed T et al. Acetaminophen for osteoarthritis. Cochrane Database of Systematic Reviews 2006.
3. Abraham et al. National Adherence to Evidence-based guidelines for the prescription nonsteroidal anti-inflammatory drugs. *Gastroenterology* 2005; 129:1171=1178.
4. Goldstein et al. Impact of Adherence to concomitant gastroprotective therapy on nonsteroidal-related Gastroduodenal Ulcer Complications. *Clin Gastroenterol Hepatol* 2006 Nov; 4(11); 1337-45

Unmet Needs with Current OA Treatments

- High levels of dissatisfaction with current therapy[1]
  - 73% of general practitioners
  - 63% of patients
- Trials with multiple agents often required
  - 53% of OA patients switch to a second NSAID within first 2 months[2]
    - Most common reason (33%) = Lack of efficacy
    - Second most common (13%) = Adverse events
  - Switching less common with selective COX-2 inhibitors [3,4]
- Critical need for additional OA treatments

1 Crichton et al. GP and patient perspectives on treatment with non-steroidal anti-inflammatory drugs for the treatment of pain in osteoarthritis. *Current Med Res Opinion* 2002; 18:92-96

2 Walker et al. Patterns of interchange in the dispensing of non-steroidal anti-inflammatory drugs. *Journal of Clinical Epidemiology* 1992; 45:187-195.

3. Rhame et al. Therapy switching and associated costs in elderly patients receiving COX-2 selective inhibitors or non-selective non-steroidal anti-inflammatory drugs in Quebec, Canada. *Rheumatology* (Oxford). 2006 45(7):903-10.

4. Zhao et al. Drug switching patterns among patients with rheumatoid arthritis and osteoarthritis. *Pharmacoepidemiol Drug Saf*. 2004 May;13(5):277-87.

Conclusions

- OA is a common, serious and disabling disease that is a growing problem.
- While current therapy provides some relief to OA patients, significant dissatisfaction persists.
- The addition of new agents, even with similar mechanisms of action, has the potential to provide additional relief for many OA patients.