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Outcome Measures for Claims to Reduce NSAID-Associated Upper Gastrointestinal (UGI) Toxicity

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DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought the discussion topic, "Outcome Measures for Claims to Reduce NSAID-Associated Upper Gastrointestinal Toxicity", to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

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1. EXECUTIVE SUMMARY

NSAIDs have been associated with toxicity to the gastrointestinal (GI) tract. Although NSAIDs have been associated with GI injury from the mouth to the anus, the upper gastrointestinal tract (UGI) is the most common site for toxicity. Several products have been studied for risk reduction of NSAID-associated UGI toxicity including misoprostol (a prostaglandin E analog that suppresses gastric acid production and has mucosal protective properties), products that suppress gastric acid secretion [e.g., proton pump inhibitors (PPIs)], and NSAIDs (e.g., COX-2 selective drugs)]. Although the focus of this Committee meeting will be to discuss toxicity involving the UGI tract, the Agency recognizes that there is NSAID-associated morbidity and mortality from lower GI tract injury. However, products that may reduce the risk of UGI toxicity (e.g. PPIs) may not necessarily reduce the risk of LGI toxicity.

The Division of Gastroenterology Products (DGP) and the Division of Anesthesia and Analgesia Products (DAAP), have used different approaches to support claims for risk reduction of NSAID-associated UGI toxicity in the past. The DGP had accepted endoscopically-proven ulcers as the primary endpoint to approve several products for the indication of risk reduction of NSAID-associated gastric ulcers (GUs) and/or duodenal ulcers (DUs). In contrast, DAAP had required clinical outcome trials using a reduction of upper gastrointestinal complications (UGICs), usually perforations, obstructions, and bleeding. To address these differences within the Agency, the Divisions met and examined the basis for the different approaches. After performing a review of cross-study comparisons of ulcers in endoscopy trials to UGICs in outcome trials of three product classes, a consensus was reached that the endoscopically demonstrated ulcers correlate with UGICs. We wish to discuss these findings with the Advisory Committee members to gain additional advice.

This document includes an overview of surrogate endpoints accepted by the Agency to support product claims and a discussion of endpoints used in clinical trials to assess NSAID-associated UGI toxicity. The methods and results of these cross-study comparisons will also be discussed in this background package.

The Committee will be asked to discuss whether endoscopically-observed ulcers can serve as a surrogate outcome measure for gastroprotective therapies for the labeled indication of risk reduction of NSAID-associated gastric ulcers and/or duodenal ulcers. Similarly, the Committee will be asked to consider whether this same endpoint is adequate for the assessment of NSAID-associated UGI complications for NSAIDs and products with novel mechanisms of action which may cause associated UGI complications. For more details see Items for Discussion in Section 9.0.

2. MORBIDITY AND MORTALITY OF NSAID-ASSOCIATED UGI INJURY

NSAIDs are associated with the following noxious effects in the GI tract: 1) decrease in duodenal mucosal bicarbonate, 2) reduction in gastric mucosal blood flow as a consequence of inhibitory

effects on the biosynthesis of protective endogenous prostaglandins; 3) prevention of the increase in cell replication at ulcer margins; and 4) inhibition of platelets hemostasis (adhesion, activation, or thrombus propagation).

Clinically, these effects may result in the formation of gastric ulcers (GUs) and/or duodenal ulcers (DUs), with or without associated symptoms. In turn, ulcers may develop serious UGI complications (UGICs) including bleeding, perforation into the peritoneal cavity, obstruction due to pre-pyloric or antral GU scarring, and penetration into adjacent solid organs. Bleeding is the most common UGIC of NSAID therapy, perforations are less common, and gastric outlet obstructions and penetrations are the least common. Although the site of NSAID-associated GI complications can be anywhere along the GI tract, the most common site is the UGI and the most common complications are upper GI bleeds from GUs and/or DUs.

Approximately 1% to 2% of NSAID users develop UGICs per year, a rate 3 to 5 times higher than non-NSAID users. The risk of severe NSAID-related UGICs is greater in patients with well-established risk factors and the case-fatality rate for patients admitted to the hospital for UGI bleeding is approximately 5%.[1] The total annual costs of all medical care for NSAID-associated GI complications in the U.S. were conservatively estimated to exceed $2 billion.[2]

3. USE OF SURROGATE ENDPOINTS TO SUPPORT EFFICACY

A surrogate endpoint is defined as a laboratory measure or marker or physical sign that is used in therapeutic trials as a substitute for a clinically meaningful endpoint that is a direct measure of how a patient feels, functions, or survives and is expected to predict the effect of the therapy. The use of surrogate endpoints may be acceptable when the pathophysiology of a disease and the mechanism of action of a therapy are very well understood. Thus, a link between specific pharmacologic effects and clinical effectiveness is needed. In certain situations, demonstration of a treatment effect on a validated surrogate endpoint can support ordinary approval. Examples of this include blood pressure effects of antihypertensive agents (reduction of stroke and myocardial infarction) or cholesterol lowering effects of lipid lowering agents (reduction of myocardial infarction and stroke). However, when pharmacologic effects on specific surrogate endpoint have not been clearly demonstrated to correlate with clinical effects, erroneous conclusions regarding the effectiveness of the drug may be drawn. For example, pharmacologic effects such as arrhythmia suppression by Type 1 antiarrhythmics and increased cardiac output by phosphodiesterase inhibitors or beta adrenergic inotropes resulted in increased mortality, rather than, as was expected, decreased sudden death and improved outcome in heart failure, respectively.[3] The utility of surrogate endpoint measures in providing independent substantiation is greatest when there is prior experience with the pharmacologic class, and the surrogate endpoint is clearly linked to clinical outcome. The Agency generally reviews the evidence for use of surrogate endpoints in clinical trials on a case by case basis, and requires clear demonstration of a link between the surrogate endpoint and clinical outcome to support use of the surrogate with a standard approval.

4. ENDPOINTS USED TO ASSESS NSAID-ASSOCIATED UPPER GI TOXICITY

Table 4.1 displays endpoints that have been used to assess NSAID-associated upper GI toxicity in clinical trials of investigational products.

Table 4.1: Endpoints to assess NSAID-associated upper GI toxicity in clinical trials

	Endpoint[1]	Frequency
1	Symptoms	8% to 40% in literature; 5% to 15% in clinical trials
2	Endoscopically-Diagnosed Ulcers	9.7% to 40% cumulative incidence for nonselective NSAIDs over 12-13 weeks in endoscopy trials
3	UGI Symptomatic Events	2.4 to 4.5 events per 100 patient-years for nonselective NSAIDs in CLASS and VIGOR
4	UGICs	0.9 to 1.4 events per 100 patient-years for nonselective NSAIDs in CLASS, VIGOR, and TARGET

1 UGICs are upper GI complications; UGI symptomatic events include UGICs and symptomatic, uncomplicated ulcers.

4.1. Symptoms

Gastrointestinal symptoms (e.g., abdominal pain, nausea, heartburn, dyspepsia) are common with NSAIDs, and are the major limiting side effects of chronic NSAID use[4,5] and have been found to be a poor predictor of UGICs. Endoscopy trials have shown that peptic ulcerations are often asymptomatic. Furthermore, only 20% of patients who developed an NSAID-associated UGIC have had warning symptoms prior to having the event. Importantly, upper GI symptoms do not correlate well with NSAID users versus nonusers.[6] Conversely, upper abdominal pain, indistinguishable from symptoms associated with classic PUD, frequently occurs in patients who have no demonstrable ulcers.[7]

4.2. Endoscopically- diagnosed Ulcers

Endoscopy trials of misoprostol, PPIs, and COX-2 selective NSAIDs used the cumulative incidence of protocol-driven, endoscopically-diagnosed ulcers as a primary endpoint to assess NSAID-associated upper GI toxicity. Most of the trials defined endoscopically-proven ulcers as a break in the mucosa of at least 3 mm in diameter with unequivocal depth. A few trials included a higher threshold for the definition of endoscopically-proven ulcers (e.g., $\geq$ 5 mm in diameter). Some trials only included GUs in the primary endpoint definition and others included both GUs and DUs. In the endoscopy trials of misoprostol and PPIs, patients received a variety of non-selective or selective NSAIDs and were randomized to the gastroprotective product or placebo. In contrast to the trials of gastroprotective products, patients in the endoscopy trials of COX-2 selective NSAIDs were randomized to the specific study drug or a nonselective NSAID. In general, patients with positive *H. pylori* status at baseline were excluded in endoscopy trials of gastroprotective products; whereas, in endoscopy trials of COX-2 inhibitors, patients were allowed to participate regardless of *H. pylori* status at baseline.

DGP has approved misoprostol and PPIs for risk reduction of NSAID-associated GUs on the basis of endoscopy trials without data from large GI outcome trials (see Section 4.0).

However, the following arguments have been made against the use of endoscopy trials to support claims for risk reduction of NSAID-associated UGI toxicity.[8,9,10,11]

1. There has been no direct evidence of a correlation of mostly asymptomatic endoscopically-diagnosed ulcers with UGICs in the same trial.
2. Ulcers in many endoscopy trials have been defined as a mucosal break of at least 3 mm in diameter; however, ulcers associated with UGICs tend to have larger diameters, over 1.0 cm. It is not known whether the use of larger diameter thresholds of endoscopically demonstrated ulcers may be more clinically-meaningful.
3. The depth of ulcers has been thought to be an important factor in developing UGICs. Ulcers that lead to an UGIC are thought to penetrate into large arteries in the submucosa to cause bleeding or through the entire gastric or duodenal wall to cause a perforation. However, endoscopic techniques used in endoscopy trials may not be able to accurately assess ulcer depth.
4. In COX-2 selective NSAID outcome trials, as many as 8% to 19% of patients with UGICs had no ulcer found on upper endoscopy (see Table A5 in Appendix 11.3).

4.3. UGI Symptomatic Events including Upper Gastrointestinal Complications (UGICs)

UGI symptomatic events include serious UGICs as well as uncomplicated symptomatic ulcers that lead to vomiting, weight loss, or severe abdominal pain, but do not progress to significant bleeding, perforation, or obstruction. Clinical outcome studies have used composite endpoints of UGICs including PUBs (perforations, symptomatic ulcers, and bleeding) and **POBs**, (perforations, obstructions and bleeding.)

UGICs are considered the gold standard to assess clinically meaningful NSAID-associated UGI toxicity in clinical trials. UGICs have been the primary endpoints in several large outcome trials of COX-2 selective NSAIDs including celecoxib and lumiracoxib, and important secondary endpoints in studies of rofecoxib and etoricoxib. (See Section 7.3 for the design of these four large COX-2 selective NSAID outcome trials.) Although UGICs are the gold standard endpoint, large GI outcome trials are challenging to conduct as the rates of UGICs are generally low and the studies require enrollment of thousands of patients, for periods of up to a year or longer, in order to demonstrate a difference in the rate of events across treatment groups.

5. DGP'S APPROACH TO GASTROPROTECTION CLAIMS

DGP has accepted endoscopically-diagnosed ulcers as the primary endpoint to support claims for products intended for gastroprotection (i.e., misoprostol, PPIs) in NSAID-treated patients. Listed below are drugs approved for risk reduction of NSAID-associated GUs and/or DUs on the sole basis of endoscopy trials.

CYTOTEC [misoprostol]	approved 1988
ARTHROTEC [diclofenac/misoprostol]	approved 1997
PREVACID [lansoprazole]	approved 2001
PREVACID NAPRA PAC [lansoprazole/naproxen]	approved 2003
NEXIUM [esomeprazole]	approved 2004
VIMOVO [esomeprazole/naproxen]	approved 2010

Although misoprostol was approved for the risk reduction of NSAID-associated GUs on the sole basis of endoscopically detected ulcers, the approval included a post marketing commitment (PMC) to evaluate the impact of misoprostol on UGICs (see Section 5.1). Subsequent gastroprotective product approvals have not required a clinical GI outcome trial as a PMC. Since the approvals of the products listed above were based on the endoscopy endpoint, labeling of these products has been limited to what was demonstrated in the clinical trials supporting approval, i.e. risk reduction of ulcers.

5.1. Misoprostol

The approval of misoprosotol was based on data from two 12-week, randomized, double-blind, placebo-controlled trials in osteoarthritis patients who required chronic NSAID treatment (Misoprostol Endoscopy Studies 1 and 2). To enter the trials, patients were required to have NSAID-associated UGI symptoms (pain) and have no ulcers on baseline upper endoscopy. Patients were randomized to misoprostol 200 µg QID, misoprostol 100 µg QID, or placebo.

In Studies 1 and 2, the mean age was 74 and 60 years old, prior history of ulcer was 18% and 7%, and the mean duration of NSAID exposure prior to study entry was 12 and 14 months, respectively. In the trials, patients were treated with: ibuprofen (1780mg/day), naproxen (880mg/day), or piroxicam (20mg/day). The primary endpoint in both trials was cumulative incidence of endoscopically-diagnosed GU, defined as greater than 3 mm in diameter, with perceptible depth, during the 12-week treatment period.

Table 5.1 and Table 5.2 display the efficacy results from the two misoprostol endoscopy trials. In both trials, the misoprostol treatment groups demonstrated a relative decrease in risk of endoscopically-proven GUs compared to the placebo groups (RR = 0.1 and 0.2, respectively). Based on these results, misoprostol was approved with the following indication:

> "reducing the risk of NSAID-induced GUs in patients at high risk of complications from GU, e.g., the elderly and patients with concomitant debilitating disease, as well as patients at high risk of developing GUs, such as patients with a history of ulcer".

Table 5.1: Endoscopically-diagnosed GUs over 12 weeks in the misoprostol trials[1]

Treatment Groups	GUs	Incidence of GUs	Comparison	RR	95% CI
Misoprostol Endoscopy Study 1 (12 weeks)					
Misoprostol 200 µg QID (n=74)	1	1%	Misoprostol (200 µg QID)/NSAID vs. NSAID	0.1	<0.1, 0.4
Misoprostol 100 µg QID (n=77)	5	7%	—	—	
Placebo (n=76)	19	25%	—	—	
Misoprostol Endoscopy Study 2 (12 weeks)					
Misoprostol 200 µg QID (n=65)	2	3%	Misoprostol (200 µg QID)/NSAID vs. NSAID	0.2	<0.1, 0.8
Misoprostol 100 µg QID (n=66)	5	8%	—	—	
Placebo (n=62)	11	18%	—	—	

[1] Misoprostol endoscopy trials in the label

After approval of misoprostol, the post-marketing commitment was addressed and a trial was conducted, called MUCOSA ("The Efficacy and Safety of Misoprostol in the Prevention of NSAID-Induced Serious GI Complications")[12]. MUCOSA was a 6-month, randomized, double-blind, placebo-controlled trial in rheumatoid arthritis patients in the U.S. or Canada who used NSAIDs chronically and were likely to require NSAIDs for the duration of the trial. Patients were allowed to receive any 1 of 10 protocol-specified NSAIDs dosed at 50-75% of the maximum approved dose, and concomitant steroids. *H. pylori* positive patients were not excluded. There were no scheduled endoscopies in this trial.

Patients were randomized to receive misoprostol 200 µg QID (the initial dose was 100 µg QID for the first 10 days) or placebo. The primary endpoint was incidence of UGICs, specifically perforations, obstructions, and bleeding. MUCOSA enrolled a much larger sample size (N=8843) than the misoprostol endoscopy trials. As shown in Table 5.2, the relative decrease in risk of UGICs in the misoprostol group compared to placebo was 0.6.

Therefore, use of misoprostol, compared to placebo, resulted in a relative decrease in the risk of endoscopically-diagnosed GUs in endoscopy trials and a relative decrease in risk of UGICs as evidenced in MUCOSA.

Table 5.2: UGICs in MUCOSA[1]

Treatment Groups	UGICs	Incidence of UGICs	Comparison	RR	95% CI
Misoprostol 200 µg QID[2] (n=4404)	25	0.6%	Misoprostol/NSAID vs. NSAID	0.6	0.3, 0.9
Placebo (n=4439)	42	1.0%			

[1] The initial misoprostol dose was 100 µg QID for 10 days then 200 µg QID.

5.2. Proton Pump Inhibitors

Registration endoscopy trials of PPIs have been 3 to 6 month, randomized, placebo-controlled and/or active-controlled trials in patients who required chronic use of NSAIDs. Patients had to have no evidence of ulcers on baseline upper endoscopy. Patients were treated with NSAIDs and were randomized to a PPI or placebo and underwent upper endoscopies to assess for GUs and DUs. Erosions (superficial lesions without depth) have not been included as an important endpoint and have not been included in labeling. This is because erosions tend to be transient and are less likely to be associated with UGICs compared to ulcers. Dyspepsia has also not been included in labeling because there has been poor correlation of NSAID-associated symptoms and UGICs (see Section 4.1).

Table 5.3 displays the GU treatment effects of approved gastroprotective products compared to placebo in endoscopy trials of NSAID-treated patients. Table 5.3 also displays the results of a published study that evaluated esomeprazole for the risk reduction of GUs in low-dose aspirin-treated patients[13] and a comparison of the risk factors for NSAID-associated UGI toxicity across the endoscopy trials.

There was a relative decrease in risk for UGICs for PPIs that ranged from 0.1 to 0.4. The difference in the incidence of ulcers between the gastroprotective products and control groups (observed risk difference) ranged from 7% to 29%. The variability in the range of risk difference may be related to the differences in the underlying risk of NSAID-associated UGI toxicity in the patient populations enrolled in the trials. Endoscopy trials which enrolled patients with lower risk of UGI toxicity, found both a lower incidence of GUs in the control group and a lower risk difference between the gastroprotective product and the control group.

In a published trial investigating the impact of esomeprazole on the use of low-dose aspirin, the relative decrease in risk of GUs was 0.3; however, the observed difference in proportion of patients who had GUs was only 3%. The Committee will be asked to discuss the clinical meaningfulness of a small decrease in risk of GUs in studies that enroll a population at low risk of NSAID-associated UGI toxicity.

Table 5.3: Risk difference and relative risk of GUs for gastroprotective products compared to placebo control in 3-6 month endoscopy trials[1]

	Incidence of GUs	Risk Difference[2]	Relative Risk (95% CI)[3]	Risk Factors	NSAIDs Used
Misoprostol ± NSAIDs					
Misoprostol Endoscopy Study 1 (12 weeks) – EGD at Weeks 0, 4, 8, and 12					
Misoprostol 200 µg QID (n=74)	1 %	24%	0.1 (<0.1, 0.4)	Mean age = 74 years old Hx of ulcer = 18%	ibuprofen, piroxicam, naproxen
Placebo (n=76)	25%				
Misoprostol Endoscopy Study 2 (12 weeks) – EGD at Weeks 0, 4, 8, and 12					
Misoprostol 200 µg QID (n=65)	3%	15%	0.2 (<0.1, 0.8)	Mean age = 60 years old Hx of ulcer = 7%	ibuprofen, piroxicam, naproxen
Placebo (n=62)	18%				
PPIs ± NSAIDs					
Lansoprazole Study (12 weeks) – EGD at Weeks 0, 4, 8, and 12					
Lansoprazole 15 mg/day (n=136)	20%	29%	0.4 (0.3, 0.6)	Mean age 60 years Hx of GU = 99% Hx of DU = 50% Low dose aspirin use = 19%	ibuprofen, piroxicam, naproxen, diclofenac
Placebo (n=133)	49%				
Esomeprazole Study 1 (26 weeks) – EGD at Weeks 0, 4, 12, and 26					
Esomeprazole 20 mg/day (n=191)	5%	7%	0.4 (0.2, 0.9)	Mean age = 64 Hx of PUB 26% Hx of POB = 1% Low dose aspirin use = 10%	COX-2 = 14% Non-selective = 85%
Placebo (n=184)	12%				
Esomeprazole Study 2 (26 weeks) – EGD at Weeks 0, 4, 12, and 26					
Esomeprazole 20 mg/day (n=267)	5%	12%	0.3 (0.1, 0.5)	Mean age = 66 Hx of PUB = 10% Hx of POB = 1% Low dose aspirin use = 12%	COX-2 = 39% Non-selective = 61%
Placebo (n=257)	17%				
Esomeprazole/Naproxen Study 1 (26 weeks) – EGD at Weeks 0, 4, 12, and 26					
Esomeprazole/naproxen (20/500 mg) BID (n=218)	4%	19%	0.2	Mean age = 60 Hx of PUB =5% Low dose aspirin use = 24%	Naproxen
Naproxen 500 mg BID (n=216)	23%				
Esomeprazole/Naproxen Study 2 (26 weeks) – EGD at Weeks 0, 4, 12, and 26					
Esomeprazole/naproxen (20/500 mg) BID (n=210)	7%	17%	0.3	Mean age = 60 Hx of PUB = 11% Low dose aspirin use = 23%	Naproxen
Naproxen 500 mg BID (n=210)	24%				
Esomeprazole ± Low-Dose Aspirin (75 to 325 mg) – 26 week study[13] EGD at Weeks 0, 8, and 26					
Esomeprazole 20 mg (n=493)	1%	3%	0.3	Mean age = 69	Low dose aspirin
Placebo (n=498)	4%				

[1] The primary endpoint for some of these endoscopy trials was the proportion of patients without GUs during the treatment period. Although in other trials, the primary endpoint was the proportion of patients free from GUs, the data are presented as the proportion of patients without GUs for consistency.

[2] The risk difference was the difference between the incidence of GUs in the control group and the gastroprotective product group.

[3] The relative risk was the incidence of GUs in the gastroprotective group divided by the incidence of GUs in the control group.

5.3. Arguments that Support Use of Endoscopy PPI Trials Alone to Obtain Claims

Extrapolation of Data from Treatment of Ulcers to Risk Reduction of Ulcers:
PPIs have been approved for many ulcer-related indications including treatment of DUs and GUs, prevention of recurrence of healed DUs, and treatment of NSAID-associated GUs in patients who continue their NSAIDs. Since the efficacy of PPIs in the treatment of ulcers is well-established, it is biologically plausible that PPIs can reduce the risk of serious UGICs resulting from GUs and DUs (e.g., greater than 3 mm in diameter).

Cross-Study Correlation between Ulcer Reduction in Endoscopy Trials with UGICs Reduction in Small, GI Outcome Trials
In endoscopy trials of PPIs in NSAID-treated patients, PPIs reduced the risk of endoscopically diagnosed ulcers compared to control group. The relative decrease in risk of GUs and/or DUs in the PPI + NSAID groups compared to the NSAID monotherapy groups ranged from 0.2 to 0.4 (see Table 5.4).

Table 5.4: Endoscopically diagnosed GUs and/or DUs in NSAID-treated patients in PPI endoscopy trials[1]

Treatment Groups	Endoscopic ulcers	Incidence of endoscopically diagnosed ulcers	Comparison	RR	95% CI
Lansoprazole Study (12 weeks)[2,3]					
Misoprostol 200 µg QID (n=106)	12	11%	—	—	
Lansoprazole 30 mg/day (n=116)	20	17%	Lansoprazole 30 mg/NSAID vs. NSAID	0.4	0.2, 0.6
Lansoprazole 15 mg/day (n=121)	23	19%	Lansoprazole 15 mg/NSAID vs. NSAID	0.4	0.3, 0.6
Placebo (n=112)	55	49%	—	—	
Esomeprazole Study 1 (6 months)					
Esomeprazole 40 mg/day (n=271)	11	4%	Esomeprazole 40 mg /NSAID vs. NSAID	0.2	0.1, 0.4
Esomeprazole 20 mg/day (n=267)	12	5%	Esomeprazole 20 mg /NSAID vs. NSAID	0.3	0.1, 0.5
Placebo (n=267)	46	17%	—	—	
Esomeprazole Study 2 (6 months)					
Esomeprazole 40 mg/day (n=196)	8	4%	Esomeprazole 40 mg /NSAID vs. NSAID	0.4	0.2, 0.8
Esomeprazole 20 mg/day (n=192)	9	5%	Esomeprazole 20 mg /NSAID vs. NSAID	0.4	0.2, 0.9
Placebo (n=185)	20	11%	—	—	
Esomeprazole/Naproxen Study 1 (6 months)[2,4]					
Esomeprazole/Naproxen (n=218)	1	5%	Esomeprazole 40 mg/ Naproxen vs. Naproxen	0.2	0.1, 0.3
Naproxen (n=216)	60	28%			
Esomeprazole/Naproxen Study 2 (6 months)[2,4]					
Esomeprazole/Naproxen (n=210)	17	8%	Esomeprazole 40 mg/ Naproxen vs. Naproxen	0.3	0.2, 0.5
Naproxen (n=210)	59	28%			

[1] These studies appear in the labels.
[2] The analysis in this table includes both GUs and DUs; however, the primary endpoint for the lansoprazole endoscopy trial and the esomeprazole/naproxen trials only included GUs. Note, the RR of GUs only in these 3 trials is the same as the RR of both GUs and DUs.
[3] The RR (95% CIs) of misoprostol µg QID/NSAID compared to lansoprazole 30 mg/NSAID was 0.7 (0.3, 1.3). The RR (95% CIs) of misoprostol µg QID/NSAID compared to lansoprazole 15 mg/NSAID was 0.6 (0.3, 1.1).
[4] Naproxen was dosed 500 mg BID, esomeprazole was dosed 20 mg BID.

Three small GI outcome trials of PPIs were conducted in Hong Kong [14,15,16]. The studies were 6 to 12 month, randomized, double-blind trials of PPIs in patients at very high risk of UGICs who were anticipated to require the use of chronic NSAIDs. All of these patients had a recent acute

UGIC (e.g., upper GI bleed or gastric outlet obstruction) that was successfully treated as evidenced by no ulcers on baseline upper endoscopy. Patients were randomized to the combination of a PPI and a specific NSAID or NSAID monotherapy. The primary endpoint for these trials was recurrent upper GI bleeding and/or other UGICs. Note, these trials were not conducted under Investigational New Drug (IND) Applications, the results were not submitted to the Agency, and the results presented in Table 5.5 are based on literature reports.

In these small GI outcome trials, the PPI + NSAID group reduced the risk of UGICs compared to the NSAID monotherapy group with a relative decrease in risk ranging from 0.1 to 0.5, with one study having no events in the PPI+NSAID arm (see Table 5.5). The RR of endoscopically diagnosed ulcers in endoscopy PPI trials was similar to the RR of UGICs in small GI outcome trials of PPIs. This cross study comparison provides support for a correlation between endoscopically diagnosed ulcers and UGICs for PPI products.

Table 5.5: Risk reduction of UGICs in Hong Kong patients at very high risk of UGICs

Treatment Groups	UGICs[1]	Incidence of UGICs	Comparison	RR	95% CI
Chan 2007[14]					
Celecoxib 200 mg BID & Esomeprazole 20 mg BID (n=137)	0	0%	Celecoxib/Esomeprazole vs. Celecoxib	0	–
Celecoxib 200 mg BID (n=136)	12	9%			
Lai 2002[15]					
ASA 100 mg & Lansoprazole 30 mg/day (n=62)	1	2%	ASA/Lansoprazole vs. ASA	0.1	<0.1, 0.8
ASA 100 mg (n=61)	9	15%			
Chan 2001 (NSAID sub-study)[16]					
Naproxen 500 mg BID & Omeprazole 20 mg/day (n=75)	3	4%	Naproxen/Omeprazole vs. Naproxen	0.2	0.1, 0.8
Naproxen 500 mg BID (n=75)	13	19%			
Chan 2001 (ASA sub-study) [16]					
ASA 80 mg & Omeprazole 20 mg/day (n=125)	1	1%	ASA/omeprazole vs. ASA	0.5	0.1, 5.4
ASA 80 mg/day (n=125)	2	2%			

ASA = low dose aspirin
[1] UGICs = the number of patients with an UGIC

Lower Incidence of UGICs in the PPI Subgroup in the MEDAL Program

Additional support for the correlation of a reduction in endoscopically diagnosed ulcers with a reduction in UGICs for PPI use in conjunction with NSAIDs is based on subgroup analyses of UGICs by PPI use in the Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL)[17] Study Program. The MEDAL Program was a pooled analysis of three randomized, double-blind, diclofenac-controlled trials of etoricoxib, a COX-2 selective NSAID, in patients with OA or RA who were anticipated to require chronic NSAID therapy. The MEDAL Program

included over 34,000 patients treated for up to 3 years (see Table 7.2 for the design of the MEDAL Program). All UGICs were adjudicated in the MEDAL Program.

In the MEDAL Program, PPI use was encouraged in patients with risk factors for GI complications (i.e., age 65 and older, prior symptomatic ulcer, or concomitant use of aspirin, anticoagulants, or steroids), but was not a randomized treatment arm. As Table 5.6 shows, etoricoxib-treated and diclofenac-treated patients who received a concomitant PPI (around 6,900 patients/treatment group) had a lower incidence of UGICs compared to patients without concomitant PPI use (about 10,000 patients/treatment group).

Table 5.6: Rate of UGICs in the MEDAL Program by PPI use[1]

	Treated Patients	UGICs	UGICs/ 100-pt year
Etoricoxib Treatment Group			
All Etoricoxib-Treated Patients	**N=17,412**	**78**	**0.30**
Concomitant PPI use	n=6,950	24	0.20
No PPI use	n=10,462	54	0.38
Diclofenac Treatment Group			
All Diclofenac-Treated Patients	**N=17,289**	**82**	**0.32**
Concomitant PPI use	n=6,906	32	0.27
No PPI use	n=10,383	50	0.36

[1] PPI use group were patients who used PPIs for at least 75% of the study period.

Table 5.7 shows that patients in the PPI use subgroups were at a higher risk of NSAID-associated UGI toxicity than patients in the non-PPI use subgroups (a greater proportion patients greater than 65 years old, with prior PUB, and on concomitant low-dose aspirin). Although the risk of UGICs was greater in the PPI subgroups, the PPI subgroups had a lower rate of UGICs than the patients who did not use PPIs. These outcomes study data support the finding of PPI use and risk reduction of UGICs.

Table 5.7: Risk factors for UGICs by PPI use subgroup

	Etoricoxib Group		Diclofenac Group	
	PPI Use	No PPI Use	PPI Use	No PPI Use
	Etoricoxib (n=6951)	Etoricoxib (n=10,461)	Diclofenac (n=69111)	Diclofenac (n=10,378)
Age > 65 years	41%	35%	41%	36%
History of UGI symptomatic event[2]	10%	4%	11%	4%
Concomitant Aspirin Use	45%	28%	45%	28%

[1] PPI use group were patients who used PPIs for at least 75% of the study period.
[2] UGI symptomatic events included complicated events (UGICs) and uncomplicated events.

6. DAAP'S APPROACH TO RISK REDUCTION CLAIMS

6.1. Regulatory History of Selective NSAIDs for Risk Reduction Claims

Traditionally, claims for less GI toxicity for NSAIDs have required clinical outcome studies. Outcomes studies for two approved COX-2 selective NSAIDs had different results. In CLASS[18], celecoxib failed to demonstrate a relative decrease in risk of UGICs compared to diclofenac and ibuprofen and was not labeled for a GI benefit, although endoscopy studies showed a decrease in risk. In VIGOR[19], rofecoxib did demonstrate a relative decrease in risk of UGICs compared to naproxen in patients who were not taking aspirin for cardioprophylaxis, consistent with endoscopy studies, and was allowed to add this claim to the labeling.

Outcome studies were also conducted for two COX-2 selective NSAIDs that were not approved in the U.S. In the MEDAL Program, etoricoxib failed to demonstrate a relative decrease in risk of UGICs compared to diclofenac, although there were fewer endoscopically diagnosed ulcers. In TARGET[20], lumiracoxib demonstrated a relative decrease in risk of UGICs compared to ibuprofen and naproxen, and fewer endocosopically diagnosed ulcers, although the relative decreases in risk of UGICs were lower than the relative decreases in risk of endoscopically diagnosed ulcers in endoscopy trials of lumiracoxib.

Given that some the endoscopy studies for these four products demonstrated fewer ulcers, but only two of the four outcome studies found a statistically significant difference in the UGICs, DAAP had continued to require the outcome studies in order to demonstrate an effect on clinically relevant endpoints to support any labeling claims.

6.2. Re-evaluation of DAAP's Approach to Support Risk Reduction Claims for Selective NSAIDs

The different regulatory approaches between DGP and DAAP were reviewed. As noted, DGP was requiring endoscopy studies to support an indication for reduction in NSAID-associated gastric ulcers for PPIs, while DAAP was requiring clinical outcome studies to support claims for less NSAID-associated GI toxicity. The divisions met to discuss the differences and develop a path forward that adequately addressed the issues associated with the various products. DAAP reviewed the results of GI outcome studies and endoscopy studies for products that had undergone evaluations with both types of studies. The methods, limitations, and results of these comparisons are presented in detail in Section 7.0.

Cross-study comparisons were evaluated and differed from prior comparisons relying only on prespecified primary endpoints by accounting for differences in important risk factors for UGI toxicity including the specific NSAIDs in the trials, the dose of the NSAID, and the use of concomitant low-dose aspirin. In addition, these comparisons attempted to minimize potential unknown differences between the trial populations by comparing the RR of UGI toxicity for the same NSAIDs across studies. After accounting for these differences, COX-2 selective NSAIDs had similar relative decreases in risk compared to non-selective NSAIDs of endoscopically ulcers and UGICs across the trials.

Given the correlations between endoscopically-diagnosed ulcers and UGICs in trials of three disparate classes (i.e., COX-2 selective NSAIDs, misoprostol, and PPIs), DAAP has concluded that it is acceptable to rely upon the results from appropriately designed endoscopy trials alone to support claims for risk reduction of UGI toxicity for COX-2 selective NSAIDs.

7. CROSS-STUDY COMPARISONS OF ENDOSCOPICALLY DIAGNOSED ULCERS AND UGICS IN OUTCOME TRIALS OF SELECTIVE AND NON-SELECTIVE NSAIDS

7.1. Methods for Cross Study Comparisons

The following are the methods used for the cross-study comparisons between the endoscopy and outcome trials of selective NSAIDs.

a. The relative risk (RR) of endoscopically diagnosed ulcers in endoscopy trials of selective NSAIDs was compared to the RR of UGICs in outcome trials of selective NSAIDs (e.g., CLASS, VIGOR, TARGET, and the MEDAL Program).

b. One major limitation of cross study comparisons is that the trials may have unknown differences in the populations enrolled that may influence the results in each trial. To minimize these potentially unknown differences, the RR of UGI toxicity between two NSAIDs within the same trial was compared to the RR of UGI toxicity between the identical NSAIDs in another trial.

c. The baseline risk factors for NSAID-associated UGI toxicity in the endoscopy and outcome trials were compared (i.e., prior UGICs, prior UGI symptomatic event, mean age, population, concomitant low-dose aspirin, type of NSAID, NSAID daily dose). In the endoscopy and outcome trials, risk factors for prior UGICs, prior UGI symptomatic event, mean age, and population were similar. However, the incidences of several important baseline risk factors for NSAID-associated UGI toxicity were different in the endoscopy and outcome trials (i.e., concomitant aspirin use, type of NSAID, and NSAID daily dose):

    1. Concomitant low-dose aspirin use varied across the endoscopy and outcome trials. All of the GI outcome trials of COX-2 selective NSAIDs (except VIGOR) had a greater incidence of concomitant low-dose aspirin use than the endoscopy trials. Given the variability of concomitant aspirin use and the differential incidence of aspirin use in the endoscopy and outcome trials, the cross-study comparisons were performed within a similar concomitant aspirin use subgroup (low or high aspirin use subgroups). For example, if an endoscopy trial had a low incidence of concomitant aspirin use (e.g., 1%) it was compared to the non-aspirin subgroup (0% aspirin use) in a corresponding outcome trial. The non-aspirin subgroups of outcome trials were large subgroups that included 6,229 to 13,918 patients and represented 76% to 79% of the overall populations. See Tables A1 and A2 in Appendix 11.1 for a presentation of the effects of concomitant low-dose aspirin on endoscopically diagnosed ulcers in endoscopy trials and Table A3 in Appendix 11.2 for the effects of concomitant low-doses aspirin on UGICs in a COX-2 inhibitor outcome trial.

2. NSAID treatment groups in the endoscopy and outcome trials had different risks of UGI toxicity (e.g., naproxen > ibuprofen > diclofenac, COX-2 selective NSAIDs). To eliminate this confounding factor, only endoscopy and outcome trials that included the identical two NSAID treatment groups were included in the analysis. The four COX-2 inhibitor outcome trials had the following eight pair-wise NSAID comparisons [celecoxib-diclofenac, celecoxib-ibuprofen, diclofenac-ibuprofen (from CLASS); rofecoxib-naproxen (from VIGOR), lumiracoxib-ibuprofen, lumiracoxib-naproxen, ibuprofen-naproxen (from TARGET), and etoricoxib-diclofenac (from the MEDAL Program). Therefore, only endoscopy trials that had one of these 8 identical NSAID combinations were selected. For example, the relative risk of rofecoxib to naproxen of UGICs in VIGOR was compared to the relative risk of endoscopically diagnosed ulcers in an endoscopy trial that included the rofecoxib and naproxen treatment groups. In contrast, the etoricoxib-diclofenac comparison was not used in this analysis because there were no adequate endoscopy trials with etoricoxib and diclofenac treatment groups.

3. Greater NSAID doses are associated with greater UGI toxicity. Therefore, the analysis included those NSAID-NSAID comparisons in which the daily dose was identical in the endoscopy and outcome trials (i.e., lumiricoxib, ibuprofen, rofecoxib, naproxen, and diclofenac). In addition, NSAID-NSAID comparisons where the nonselective NSAID had the identical dose and COX-2 inhibitor had a different dose were included in the analysis (celecoxib 800 mg/day in CLASS but 400 mg/day in the endoscopy trials). The comparisons with identical NSAID-NSAID daily doses were evaluated separately from the NSAID-celecoxib comparisons because the celecoxib daily dose differed in the endoscopy and outcome trials.

d. There are dozens of endoscopy studies that assessed endoscopically diagnosed ulcers in NSAID-treated patients. We selected randomized, active-controlled trials of NSAIDs at least 12 weeks in duration in patients anticipated requiring chronic NSAIDs from a search of the published literature, recent NDA submissions for selective and nonselective NSAIDs, and Arthritis Advisory Committee Briefing Packages. The trials had to have a primary endpoint of protocol-driven, endoscopically diagnosed ulcers. Endoscopy trials investigating gastroprotective products (e.g., PPIs, H_2 antagonists, misoprostol) were not included in our analysis. The search produced 19 endoscopy trials of NSAIDs (for more details on the methods to select endoscopy trials see Section 7.4.1). Of the 19 endoscopy trials in the literature, 5 trials were selected because they had identical NSAID-NSAID treatment groups as one of the four GI outcome trials of COX-2 selective NSAIDs (see Section 7.4.1).

7.2. Limitations of Cross-Study Comparisons

In general, there are multiple limitations of cross-study comparisons because differences may exist in the conduct, treatment groups, populations, and other design features of the trials. Table 7.1 presents possible limitations of the cross-study comparisons of endoscopy and outcome trials and how we attempted to overcome these limitations.

Table 7.1: Limitations of cross study comparisons

	Limitations of Cross Study Comparisons	Attempts to Overcome the Limitations
1	The endoscopy and outcome trials used different methods for detecting the safety outcomes (protocol-driven, upper endoscopy vs. observed, adjudicated, clinically meaningful complications).	None.
2	The endoscopy and outcome trials were of different durations (12-13 weeks compared to 1-3 years). The risk of NSAID-associated GI endoscopically diagnosed ulcers and UGIC may be different at these different time points.	None.
Risks of UGICs		
3	Different NSAIDs have different risks of UGICs (e.g., naproxen vs. diclofenac).	Endoscopy trials were selected if they had identical pair-wise NSAID treatment groups as one of the COX-2 inhibitor outcome trials.
4	Higher NSAID doses are associated with a greater risk of UGICs.	Endoscopy trials were selected if they had identical dosing regimens as one of the COX-2 inhibitor outcome trials. However, since there were no endoscopy trials that included the celecoxib 400 mg BID dose (the celecoxib dose in CLASS) and diclofenac or ibuprofen (the comparators in CLASS), endoscopy trials that included the celecoxib 200 BID dose and diclofenac or ibuprofen comparator were included.
5	Different populations may have different risks of UGICs.	Only endoscopy trials were selected that included OA and/or RA patients.
6	The concomitant use of aspirin is a strong risk factor for UGICs.[1]	Comparisons were made within two subgroups that had a similar exposure to aspirin (low and high aspirin use subgroups).
7	Increased age and prior history of symptomatic ulcers are strong risk factors for UGICs.	The proportions of patients with these risk factors were generally similar across the trials. See Table 7.7 for a cross-study comparison of risk factors.

[1] See Tables A1 and A2 in Appendix 11.1 for a presentation of the effects of concomitant low-dose aspirin on endoscopically diagnosed ulcers in endoscopy trials and Table A3 in Appendix 11.2 for the effects of concomitant low-doses aspirin on UGICs in a COX-2 inhibitor outcome trial.

7.3. Outcome Trials of Selective NSAIDS

7.3.1. Design of COX-2 Inhibitor Outcome Trials

There have been 4 large GI outcome trials of COX-2 selective NSAIDs (at least 6 months in duration), i.e., CLASS, VIGOR, TARGET, and the MEDAL Program (see Table 7.2). These trials were randomized, double-blind, active-controlled, multi-centered, trials of COX-2 selective NSAIDs in OA and RA patients who were anticipated to require chronic NSAID therapy. Trials that included a gastroprotective product as a treatment group were excluded (e.g., MUCOSA). In almost all of these trials, the COX-2 inhibitor dose that was used was two to four times the approved/proposed dose for the treatment of RA and OA, respectively. In all of these trials, UGICs were pre-specified important endpoints and all UGICs were adjudicated by pre-specified criteria. In all of these trials, no baseline upper endoscopy was performed. The allowed use of concomitant low-dose aspirin differed in the trials and ranged from the exclusion of concomitant aspirin in VIGOR to the encouragement of concomitant

low-dose aspirin in the MEDAL Program in patients with vascular disease or diabetes. In CLASS, VIGOR, and TARGET, PPI use was prohibited throughout the treatment period; however, in the MEDAL program, PPI use was encouraged in patients with risk factors for GI complications (i.e., age ≥ 65, prior symptomatic ulcer, or concomitant use of aspirin, anticoagulants, or steroids).

Table 7.2: Design of the four large COX-2 selective NSAIDs outcome trials in patients anticipated to require chronic NSAIDs

Outcome Trial[1]	Years Conducted (duration)	Design	Concomitant Aspirin Use	Treatment Groups	N
CLASS	1998-2000 (13 months)	U.S. & Canadian Phase 4 trial of celecoxib in OA & RA patients	≤ 325 mg/day allowed	celecoxib 400 mg BID diclofenac 75 mg BID ibuprofen 800 mg TID	7,968
VIGOR	1999-2000 (13 months)	Global Phase 4 trial (22 countries) of rofecoxib in RA patients	No concomitant ASA use allowed	rofecoxib 50 mg/day naproxen 500 mg BID	8,076
TARGET	2001-2002 (12 months)	Global Phase 3 trial (29 countries) of lumiracoxib in OA patients	75-100 mg/day allowed)	lumiracoxib 400 mg/day ibuprofen 800 mg TID naproxen 500 mg BID	18,244
MEDAL Program	2002-2006 (36 months)	Global Phase 3 trial (38 countries) of etoricoxib in OA & RA patients	≤ 100 mg/day was strongly encouraged for vascular patients	etoricoxib 60/90 mg/day diclofenac 75 mg BID or 50 mg TID	34,701

[1] CLASS is the "Celecoxib Long-term Arthritis Safety Study", VIGOR is "Vioxx GI Outcomes Research" Study, TARGET is "Therapeutic Arthritis Research and Gastrointestinal Event Trial", and the MEDAL Program is "Multinational Etoricoxib and Diclofenac Arthritis Long-term" Study Program.

7.3.2. Risk Factors for UGI Toxicity in the COX-2 Inhibitor Outcome Trials

Table A4 in Appendix 11.3 displays the major baseline risk factors for UGICs in the 4 COX-2 inhibitor trials. The baseline risk factors for UGIC were similar in all treatment groups. See Table 7.7 for a comparison of the risk factors in the 4 COX-2 inhibitor outcome trials and the selected COX-2 inhibitor endoscopy trials.

7.3.3. Types of UGICs in the COX-2 Inhibitor Outcome Trials

Table A5 in Appendix 11.3 displays the types of overall UGICs in the four COX-2 inhibitor trials and Table 7.3 presents UGICs by treatment group in the four COX-2 inhibitor trials. In the outcome trials of COX-2 selective NSAIDs, 81% to 92% of the UGICs were due to ulcers (i.e., gastric or duodenal bleeds, perforations, or obstruction) and 8% to 19% of the UGICs were due to non-ulcer etiologies (e.g., erosions).

7.3.4. Relative Risk of UGICs in the COX-2 Inhibitor Outcome Trials

Table 7.3 displays the relative risk (RR) of UGICs in the four COX-2 inhibitor outcome trials in the entire study population and in the non-aspirin subgroup (i.e., patients who did not receive concomitant aspirin in the treatment period).

In CLASS, celecoxib did not reduce the RR of UGICs compared to diclofenac and ibuprofen. However, in the non-aspirin subgroup, celecoxib reduced the risk of UGICs compared to ibuprofen, and diclofenac reduced the risk of UGIC compared to ibuprofen.

In VIGOR, rofecoxib reduced the RR of UGICs compared to naproxen. However, since VIGOR excluded the use of concomitant aspirin, the risk reduction of UGICs of rofecoxib compared to naproxen in this important population is not known.

In TARGET, lumiracoxib reduced the RR of UGICs compared to ibuprofen and naproxen. The magnitude of lumiracoxib's risk reduction in UGICs was greater in the non-aspirin subgroup compared to the aspirin subgroup.

In the MEDAL Program, etoricoxib did not reduce the risk of UGICs in the entire population or the non-aspirin subgroup compared to diclofenac. Since diclofenac may have similar COX-selectivity as traditional COX-2 selective NSAIDs, these results are not surprising.

Table 7.3: RR of UGICs in the 4 COX-2 inhibitor outcome trials (in the entire study and non-aspirin subgroup)[1]

Population	Treatment Group	UGICs	Treated Patients	n/N	UGICs/ 100 pt-years	Comparison	RR	95% CI
CLASS								
All Patients	celecoxib	17	3,987	0.4%	0.7	celecoxib ─ diclofenac celecoxib ─ ibuprofen	0.9 0.8	**0.4, 1.9** **0.4, 1.6**
	diclofenac	10	1,996	0.5%	0.9	diclofenac ─ ibuprofen	0.9	**0.4, 2.1**
	ibuprofen	11	1,985	0.6%	1.0	─	─	
Non-ASA Subgroup	celecoxib	8	3,105	0.3%	0.4	celecoxib ─ diclofenac celecoxib ─ ibuprofen	1.0 0.4	**0.3, 3.3** **0.2, 1.0**
	diclofenac	4	1,551	0.3%	0.5	diclofenac ─ ibuprofen	0.4	**0.1, 1.3**
	ibuprofen	10	1,573	0.6%	1.1	─	─	
VIGOR								
All Patients[1]	rofecoxib	16	4,047	0.4%	0.6	rofecoxib ─ naproxen	0.4	**0.2, 0.8**
	naproxen	37	4,029	0.9%	1.4	─	─	
TARGET								
All Patients	lumiracoxib	29	9,117	0.3%	0.4	lumiracoxib -ibuprofen lumiracoxib-naproxen	0.4 0.3	**0.3, 0.7** **0.2, 0.5**
	ibuprofen	33	4,397	0.8%	1.1	─	─	
	naproxen	50	4,730	1.1%	1.4	─	─	
Non-ASA Subgroup	lumiracoxib	14	6,950	0.2%	0.3	lumiracoxib-ibuprofen lumiracoxib-naproxen	0.3 0.2	0**.1, 0.5** **0.1, 0.4**
	ibuprofen	28	3,431	0.8%	1.1	─	─	
	naproxen	36	3,537	1.0%	1.4	─	─	
MEDAL Program								
All Patients	etoricoxib	78	17,412	0.5%	0.3	etoricoxib ─ diclofenac	0.9	**0.7, 1.3**
	diclofenac	82	17, 289	0.5%	0.3	─	─	
Non-ASA Subgroup	etoricoxib	28	11,660	0.2%	0.2	etoricoxib ─ diclofenac	0.9	**0.6, 1.6**
	diclofenac	30	11,609	0.3%	0.2	─	─	

[1] In VIGOR, patients were prohibited from the use of concomitant aspirin (0% of patients used concomitant aspirin in the treatment period in VIGOR). Thus, the non-aspirin subgroup included the entire patient population in VIGOR.

Reference: Adapted from the Final Study Reports of CLASS, VIGOR, TARGET, and the MEDAL Program

7.4. Endoscopy Trials of Selective and Non-Selective NSAIDs

7.4.1. Methods to Select Endoscopy Trials of NSAIDs for Cross-Study Comparisons to Outcome Trials

There are dozens of endoscopy studies of selective and nonselective NSAIDs. To perform cross-study comparisons with the outcome trials of COX-2 inhibitor, the following sources were searched for endoscopy trials of NSAIDs:

- Literature search of English language journals in PubMed, Medline, and EMBASE from June 1987 to June 2007[21]
- Original NDA submissions of celecoxib, rofecoxib, valdecoxib, lumiracoxib, etoricoxib, and meloxicam.
- Supplemental celecoxib NDA submission for CLASS and supplemental rofecoxib NDA submission for VIGOR.
- Arthritis Advisory Committee Meeting Briefing Packages:
  - 12/1/98 – celecoxib NDA application
  - 4/20/99 – rofecoxib NDA application
  - 2/7/01 – discussion of CLASS
  - 2/8/01 – discussion of VIGOR
  - 2/16/05-2/18/05 – NSAID-associated CV toxicity
  - 4/12/07 – etoricoxib NDA application.

The eligibility criteria for selection of endoscopy trials were the following:

1. Inclusion of all randomized, active-controlled trials of NSAIDs and/or COX-2 selective NSAIDs with a primary end point of protocol-driven endoscopically diagnosed ulcers.
2. Exclusion of all trials of gastroprotective products (e.g., proton pump inhibitors, H_2-receptor antagonists, misoprostol).
3. Inclusion of trials at least 12 weeks in duration.
4. Inclusion of patients (e.g., OA, RA) anticipated requiring NSAIDs for length of study.
5. Patients had to have a baseline upper endoscopy with no baseline ulcers and needed at least one post-baseline EGD post-treatment at 12 weeks or later.
6. Trials had to have two NSAID treatment groups that were identical to 1 of the 8 pair-wise NSAID comparisons in an outcome trial [celecoxib-diclofenac, celecoxib-ibuprofen, diclofenac-ibuprofen (in CLASS); rofecoxib-naproxen (in VIGOR), lumiracoxib-ibuprofen, lumiracoxib-naproxen, ibuprofen-naproxen (in TARGET), or etoricoxib-diclofenac (in the MEDAL Program).
7. The NSAID doses had to be identical or very similar.

Using criteria #1 through #4, the search produced 19 endoscopy trials of COX-2 selective NSAIDs or non-selective NSAIDs (see Table A6 in Appendix 11.4 for a list of the 19 trials). After applying criteria #5 through #7, 5 trials were selected. Therefore, only 5 of the 19 endoscopy trials had an identical pair-wise NSAID-NSAID comparison to an outcome trial, with baseline and post-treatment upper endoscopies, and identical to very similar NSAID doses. The results of 14 endoscopy trials that did not meet criteria #7 were consistent with the results of the five selected trials that meet all 7 criteria.

In the 5 trials, all of the pair-wise NSAID comparators had identical dosing regimens in the endoscopy and outcome trials except for celecoxib (i.e., the celecoxib dosage regimen in the endoscopy trials was 200 mg BID and the celecoxib dosage regimen in CLASS was 400 mg BID). There were no well-controlled 12-week celecoxib endoscopy trials that compared celecoxib 400 mg BID to either diclofenac or ibuprofen (i.e., the two NSAID comparators in CLASS).

Table 7.4: Five endoscopy trials of COX-2 selective NSAIDs with at least one identical pair-wise comparison as an outcome trial[1]

EGD Trial (Study #)	Design (EGD Frequency)	Treatment Groups	N[2]
celecoxib-1 (N49-98-06-071)	12 week trial of celecoxib in OA and RA patients (Baseline, Weeks 4, 8, & 12)	celecoxib 200 mg BID diclofenac 75 mg BID ibuprofen 800 mg TID	1062
rofecoxib-1 (098C)	12 week trial of rofecoxib in RA patients (Baseline, Weeks 6 & 12)	rofecoxib 50 mg naproxen 500 mg BID placebo	633
valdecoxib-1 (N91-00-26-048)	12 week trial of valdecoxib OA patients (Baseline & Week 12)	diclofenac 75 mg BID ibuprofen 800 mg TID valdecoxib 10 mg valdecoxib 20 mg placebo	936
lumiracoxib-1 (CCOX189-0110)	13 week trial of lumiracoxib RA patients (Baseline, Weeks 8 & 13)	lumiracoxib 400 mg q d lumiracoxib 800 mg q d celecoxib 200 mg BID ibuprofen 800 mg TID	831
lumiracoxib-2 (CCOX189-0126)	13 week trial of lumiracoxib OA patients (Baseline, Weeks 8 & 13)	lumiracoxib 400 mg q d lumiracoxib 200 mg q d celecoxib 200 mg q d ibuprofen 800 mg TID	1011

[1] These 5 trials are a subset of the 19 endoscopy trials from Table A6 in Appendix 11.4. These trials had to have two NSAIDs that were identical to two NSAIDs in 1 of the 4 COX-2 inhibitor outcome trials. The doses of the NSAIDs had to be identical to the corresponding NSAID in the COX-2 inhibitor outcome trial (the only exception was celecoxib). All trials were randomized, double-blind, active controlled in OA and/or RA patients anticipated to require chronic NSAIDs. All patients had to have no baseline GUs or DUs. Primary efficacy endpoint was cumulative incidence of GUs and/or DUs over treatment period.

[2] N is the number of endoscopy evaluable patients in the trial (treated patients with at least one post-baseline endoscopy)

7.4.2. Baseline Risk Factors for UGI Toxicity for the Selected Endoscopy Trials

Table A7 in Appendix 11.4 presents the baseline risk factors for UGICs in the five selected COX-2 inhibitor endoscopy trials. The baseline risk factors in the five trials were similar across the treatment groups. See Table 7.7 for a comparison of baseline risk factors for NSAID-associated UGI toxicity in the endoscopy and outcome trials.

7.4.3. Relative Risk of Endoscopically diagnosed GUs and/or DUs in the Selected Endoscopy Trials

Table 7.5 delineates the RR risk of endoscopically diagnosed GUs and/or DUs for the NSAID-NSAID pair-wise comparisons in the 5 selected endoscopy trials. See Tables 7.8 and 7.9 for a comparison of the RR of endoscopically diagnosed ulcers in these endoscopy trials with the RR of UGICs in the outcome trials.

Table 7.5: Relative risk of endoscopically diagnosed GUs and/or DUs in the 5 selected endoscopy trials of COX-2 selective NSAIDs

EGD Trial (Study #)	Treatment Groups[1]	Endoscopically diagnosed Ulcers	Incidence[2]	Comparison	RR	95% CI
celecoxib-1 (N49-98-06-071)	celecoxib 200 mg BID (n=356)	25	7%	celecoxib – diclofenac celecoxib – ibuprofen	0.7 0.3	0.4, 1.2 0.2, 0.5
	diclofenac 75 mg BID (n=372)	36	10%	–	–	
	ibuprofen 800 mg TID (n=334)	78	23%	–	–	
rofecoxib-1 (098C)	rofecoxib 50 mg (n=211)	14	7%	rofecoxib – naproxen	0.3	0.2, 0.5
	naproxen 500 mg BID (n=210)	51	26%	–	–	
	placebo(n=212)	6	3%	–	–	
valdecoxib-1 (N91-00-26-048)	diclofenac 75 mg BID (n=187)	25	13%	diclofenac – ibuprofen	1.0	0.6, 1.7
	ibuprofen 800 mg TID (n=184)	25	14%	–	–	
	valdecoxib 10 mg (n=189)	7	4%	–	–	
	valdecoxib 20 mg (n=198)	7	4%	–	–	
	placebo (n=178)	8	5%	–	–	
lumiracoxib-1 (CCOX189-0110)	lumiracoxib 400 mg/day (n=212)	6	3%	lumiracoxib – ibuprofen	0.2	0.1, 0.5
	lumiracoxib 800 mg/day (n=207)	9	4%	–	–	
	celecoxib 200 mg BID (n=213)	4	2%	celecoxib – ibuprofen	0.1	0.1, 0.4
	ibuprofen 800 mg TID (n=199)	27	14%	–	–	
lumiracoxib-2 (CCOX189-0126)	lumiracoxib 400 mg q d (n=253)	10	4%	lumiracoxib – ibuprofen	0.3	0.1, 0.5
	lumiracoxib 200 mg q d (n=257)	11	4%	–	–	
	celecoxib 200 mg q d (n=253)	8	3%	–	–	
	ibuprofen 800 mg TID (n=248)	39	16%	–	–	

[1] Population were patients who were endoscopy evaluable
[2] Cumulative risk over the treatment period (patients with events in the treatment period/endoscopy evaluable patients).

7.5. Comparison of Endoscopy and Outcome Trials of Selective and Non-Selective NSAIDs

7.5.1. Comparison of Designs and Baseline Risk Factors of the Endoscopy and Outcome Trials:

Table 7.6 compares the designs of the 5 selected endoscopy trials of COX-2 selective NSAIDs to the designs of the 4 outcome trials. Both types of trials were adequate and well-controlled trials in a similar population (OA and RA patients anticipated to require chronic NSAIDs). However, the trials differed on the duration (3 month vs. 1-3 years), number of patients (600-1100 vs. 8,000 to 35,000), methods (timing and reasons for upper endoscopies), endpoints, statistical populations, and concomitant use of low-dose aspirin.

Table 7.6: Designs of the 5 selected endoscopy trials and the 4 outcome trials

	5 Selected Endoscopy Trials	4 Outcome Trials
Similarities		
Control Group	R, DB, active-controlled	R, DB, active-controlled
Population	OA & RA anticipated to require chronic NSAIDs	OA & RA anticipated to require chronic NSAIDs
Differences		
Duration	12-13 weeks	1-3 years
Number of patients	600 to 1100	8,000 to 35,000
Baseline Endoscopy	Yes	No
Endoscopy During Treatment	Both protocol-driven time points & for cause	For cause
Important Endpoint	≥ 3 mm Endoscopically diagnosed Ulcers	UGICs
Adjudication of Endpoint	No	Yes
Statistical Population	Patients who had at least one post-baseline endoscopy	Treated Patients
Concomitant ASA Use	Varied	Varied

Increased age, history of a prior UGIC, history of a prior UGI symptomatic event, and concomitant aspirin use are some of the most important risk factors for the development of NSAID-associated UGI toxicity. To address differences in the risks of NSAID-associated UGI toxicity, risk factors were compared in the endoscopy and outcome trials. Table 7.7 presents a comparison of the risk factors for NSAID-associated UGI toxicity in the five selected endoscopy trials and the four outcome trials. The baseline risk factors of age, prior UGICs, and prior UGI symptomatic event were generally similar across the trials. However, in 3 out of the 4 outcome trials (i.e., CLASS, TARGET, and the MEDAL Program), concomitant low-dose aspirin use was greater than in the 5 endoscopy trials.

Concomitant use of low-dose aspirin with a COX-2 inhibitor reduces or eliminates the potential benefit of reduction of UGI toxicity. See Tables A1 and A2 in Appendix 11.1 for a presentation of the effects of concomitant low-dose aspirin on endoscopically diagnosed ulcers in endoscopy trials and Table A3 in Appendix 11.2 for the effects of concomitant low-doses aspirin on UGICs in a COX-2 inhibitor outcome trial. Given the differential use of concomitant low-dose aspirin in the endoscopy and outcome trials, cross-study comparisons were performed within a similar concomitant aspirin use subgroup (low or high aspirin use subgroups). For example, if an endoscopy trial had a low incidence of concomitant aspirin use (e.g., 1%) it was compared to the non-aspirin subgroup (0% aspirin use) in a corresponding outcome trial. The non-aspirin subgroups in outcome trials were large subgroups that included 6,229 to 13,918 patients and represented 76% to 79% of the overall populations.

Table 7.7: Comparison of the baseline risk factors for UGICs in the 5 selected endoscopy trials and the 4 outcome trials[1]

Risk Factor	5 Selected Endoscopy Trials	4 Outcome Trials
Similarities		
Prior UGIC	**0% to 2%**	**0% to 3%**
Mean Age	**52 to 60 years**	**58 to 63 years**
Prior UGI Symptomatic Event	**6% to 13%**	**3% to 8%**
Population	**OA and RA**	**OA and RA**
Differences		
Concomitant Low-Dose ASA Use	**1% to 15%**	**0% to 35%[2]**

[1] Range of risk factors. The risk factors were well-balanced across treatment groups in the trials.

[2] In CLASS, TARGET, and the MEDAL Program, the use of concomitant low-dose aspirin was 21%, 24%, and 35%, respectively (the use of low-dose aspirin in VIGOR was 0% because aspirin use was prohibited in this trial).

7.5.2. Comparison of Endoscopically diagnosed Ulcers in Endoscopy Trials with UGICs in Outcome Trials

Given that higher NSAID doses have been associated with greater UGI toxicity and the celecoxib daily dose was higher in the outcome trial than the endoscopy trials (800 vs. 400 mg), the cross study comparisons were divided into two subgroups (i.e., identical NSAID-NSAID dosing regimens vs. identical non-selective NSAID dosing regimen but different celecoxib dosing regimen). Given concomitant low-dose aspirin use is a strong risk factor for UGI toxicity and there was a differential use of concomitant low-dose aspirin use across the trials, the cross study comparisons were divided into two aspirin subgroups (low use vs. high use).

Table 7.8 shows the RR of endoscopically diagnosed ulcers in endoscopy trials compared to the RR of UGICs in outcome trials by concomitant low-dose aspirin use subgroup (low use vs. high use). In Table 7.8, the doses of the NSAIDs were identical in the endoscopy and outcome trials ─ diclofenac (i.e., 75 mg BID), ibuprofen (i.e., 800 mg TID), rofecoxib (50 mg once daily), naproxen (500 mg BID), and lumiracoxib (i.e., 400 mg once daily). See Tables A8, A9, A10, and A11 in Appendix 11.5 for details on these 4 cross-study comparisons. For these 4 comparisons, the similarities in the RRs for ulcers and UGICs in the trials appear to support the use of appropriately designed endoscopy trials to support risk reduction of NSAID-associated UGI toxicity claims.

Table 7.8: Comparison of the RR of endoscopically diagnosed ulcers in endoscopy trials with RR of UGICs in outcome trials (identical NSAID-NSAID dose regimens)[1]

Comparison	Endoscopically diagnosed Ulcers in Endoscopy Trials			UGICs in Outcome Trials		
	Trial	ASA use	RR	Trial	ASA use	RR
Low Aspirin Use Subgroup (0% to 4%)						
lumiracoxib-ibuprofen	Lumiracoxib-1	1%	0.2	TARGET	0%	0.3
	Lumiracoxib-2	4%	0.3	(non-ASA)	0%	0.3
rofecoxib ─ naproxen	Rofecoxib-1	1%	0.3	VIGOR	0%	0.4
High Aspirin Use Subgroup (12% to 21%)						
diclofenac ─ ibuprofen	Valdecoxib-1	15%	1.0	CLASS	21%	0.9

[1] lumiracoxib (i.e., 400 mg once daily), ibuprofen (i.e., 800 mg TID), rofecoxib (50 mg once daily), naproxen (500 mg BID), & diclofenac (i.e., 75 mg BID) dose regimen were identical in the endoscopy and outcome trials.

Table 7.9 shows the RR of endoscopically diagnosed ulcers in endoscopy trials compared to the RR of UGICs in outcome trials by concomitant low-dose aspirin use subgroup (low use vs. high use). In Table 7.9, the doses of the non-selective NSAIDs were identical in the endoscopy and outcome trials [ibuprofen dose regimen (i.e., 800 mg TID) and diclofenac dose regimen (i.e., 75 mg BID)]; however, the celecoxib daily dose regimens were greater in CLASS than the endoscopy trials (i.e., 800 mg vs. 400 mg). See Tables A12, A13, and A14 in Appendix 11.5 for details on these 3 cross-study comparisons. The RRs for endoscopically diagnosed ulcers and UGICs appeared to be similar, even though the risk reduction of UGICs in CLASS was less than the risk reduction of endoscopically diagnosed ulcers in the endoscopy trials. This was most likely due to the greater dose of celecoxib in CLASS (800 vs. 400 mg) and the higher use of concomitant low-dose aspirin use in CLASS than one of the endoscopy trials (Study Celecoxib-1).

Overall, the similarities in the RRs for ulcers and UGICs in the trials appear to support the use of appropriately designed endoscopy trials to support risk reduction of NSAID-associated UGI toxicity claims.

Table 7.9: Comparison of the RR of endoscopically diagnosed ulcers in endoscopy trials with RR of UGICs in outcome trials (identical ibuprofen and diclofenac dose regimens, but different celecoxib dose regimens)[1]

Comparison	Endoscopically diagnosed Ulcers in Endoscopy Trials			UGICs in Outcome Trials		
	Trial	ASA use	RR	Trial	ASA use	RR
Low Aspirin Use Subgroup (0% to 4%)						
celecoxib – ibuprofen	Lumiracoxib-1	1%	0.1	CLASS (non-ASA)	0%	0.4
High Aspirin Use Subgroup (12% to 21%)						
celecoxib – ibuprofen	Celecoxib-1	12%	0.3	CLASS	21%	0.8
celecoxib – diclofenac	Celecoxib-1	12%	0.7	CLASS	21%	0.9

[1] The ibuprofen dose regimen (i.e., 800 mg TID) & diclofenac (i.e., 75 mg BID) dose regimen were identical in the endoscopy and outcome trials; however, the celecoxib dose regimens were greater in CLASS than endoscopy trials (i.e., 400 mg BID vs. 200 mg BID).

8. NSAID-ASSOCIATED LOWER GI INJURY AND ITS ASSESSMENT

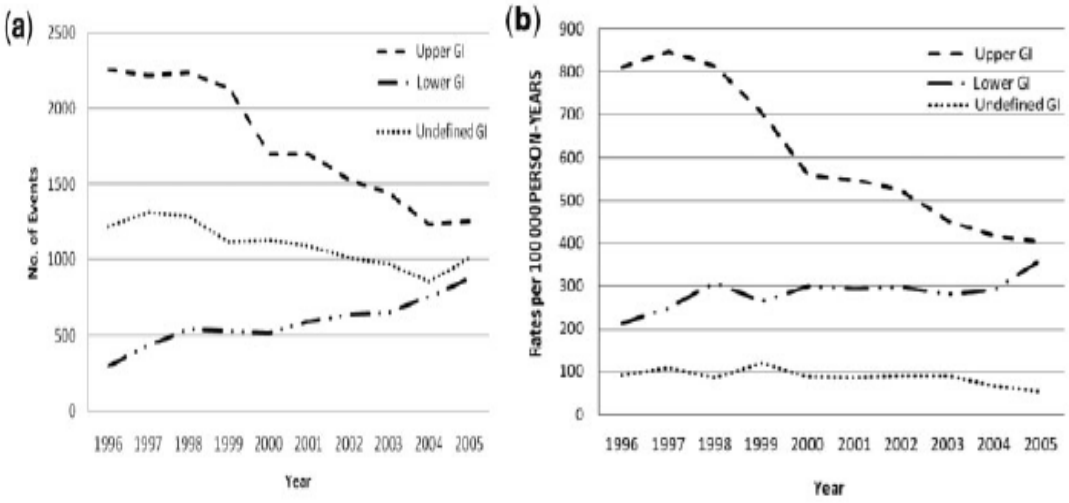
Data from observational trials suggest that lower GI complications (LGICs) are relatively common in NSAID users and that COX-2 selective inhibitors are associated with a lower risk of these events. The lower GI damage includes increased mucosal permeability, mucosal inflammation, overt or occult blood loss, malabsorption, protein loss, ileal dysfunction, diarrhea, ulceration, strictures, major bleeding and perforation.[22]

Although serious LGICs such as perforation or overt bleeding are of major clinical concern because of their life-threatening nature, events that are less severe or even asymptomatic can still have a marked impact on the patient. For example, occult blood loss or anemia can result in impaired physical performance (shorter physical performance battery scores, lower knee extensor strength and handgrip strength) and diminished quality of life

The past decade has seen major advances in the prevention and management of ulcer complications, such as a decrease in the prevalence of *H. pylori* infection and improved treatment of acute ulcer bleeding. Recent evidence suggests that these developments have been reflected in a change in the pattern of NSAID-related GI complications seen in clinical practice.[23] Thus, while the incidence of complications involving the UGI tract has decreased steadily during the last decade, perforations and bleeding in the lower GI tract have increased (see Figure 1 for the type of GI complications in Spain from 1996 to 2005).

While LGI Complications are not related to the acid peptic mechanism of injury, and PPIs are not expected to protect NSAIDs-associated lower GI adverse events, there is need to investigate lower GI injury during future clinical trials where the protective mechanism of action is not acid reduction i.e. selective NSAIDs.

Figure 1: GI complications per year in Spain (1996-2005)



(a) Total number of GI complications per year
(b) Estimated incidence of GI complications (per 100 000 person-years)

9. ISSUES/QUESTIONS FOR CONSIDERATION BY THE COMMITTEE

The questions listed below have been designed to draw you attention to issues implicit to answering the final set of questions that will be discussed at the AC.

1.) Adequacy of endoscopically diagnosed ulcers as a surrogate for UGICs

There have been no trials directly linking the reduction of endoscopically diagnosed ulcers to reduction of UGICs. However, cross-study comparisons have shown similar relative decreases of risk of endoscopically diagnosed ulcers and UGICs for three different product classes (i.e., misoprostol, PPIs, and COX-2 selective NSAIDs). Discuss whether endoscopically diagnosed ulcers alone (without outcome trials) can serve as a surrogate for UGICs considering the strengths and limitations of the cross-study comparisons for the following product classes:

- Gastroprotective products (i.e., misoprostol, PPIs)
- NSAIDs (e.g., COX-2 selective NSAIDs)
- Novel investigative products with new mechanisms of action

2.) If endoscopically diagnosed ulcers <u>are</u> adequate surrogates for UGICs for one or more product classes then consider the following:

<u>a.) Treatment Effects</u>
Endoscopy trials of gastroprotective products in patients at risk of NSAID-associated UGI toxicity have demonstrated a relative decrease in risk of endoscopically diagnosed ulcers compared to control (RR between 0.2 to 0.4) and about a 15 to 20% risk difference from control.

An endoscopy trial evaluated efficacy of PPI (esomeprazole), in low risk patients i.e. patients receiving low dose aspirin (81 to 325 mg daily) as prophylaxis for cardiovascular protection. In this trial, the risk difference of the gastroprotective product compared to control was small (e.g., 3%). However, the results demonstrated a relative decrease in endoscopically diagnosed ulcer risk compared to control (RR around 0.3).

Discuss the clinical meaningfulness of these treatment effects for a surrogate endpoint.

b.) NSAIDs in Endoscopy Trials

NSAIDs have different risks of UGI toxicity (e.g., naproxen > ibuprofen > diclofenac, COX-2 selective NSAIDs). Some products have demonstrated a relative decrease in risk of UGI toxicity in naproxen-treated patients. However, these products did not decrease the risk of UGI toxicity in patients treated with NSAIDs that are associated with lower GI risk (e.g., diclofenac, COX-2 inhibitors).

Discuss the need to demonstrate treatment benefits in endoscopy trials of patients treated with NSAIDs that are associated with lower GI risk.

c.) Duration of Endoscopy Trials

Discuss the appropriate length of endoscopy trials (e.g., 3 vs. 6 months) in light of the cross-study correlations of 3-month endoscopy trials of COX-2 selective NSAIDs with 1-3 year outcome trials of COX-2 selective NSAIDs,

3.) If endoscopically diagnosed ulcers <u>are not</u> adequate surrogates for UGICs for one or more product classes, then consider the following:

Additional Evidence Needed

Discuss what additional evidence is required to demonstrate risk reduction of UGICs prior to approval (e.g., large GI outcome trials to assess UGICs, UGI symptomatic events, or other composite endpoints) for the following three product classes (if applicable).

- Gastroprotective products (i.e., misoprostol, PPIs)
- NSAIDs (e.g., COX-2 selective NSAIDs)
- Novel investigative products with new mechanisms of action

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11. APPENDIX

11.1. Appendix – Effect of Aspirin on Ulcers in Endoscopy Trials

Table A1 shows the RR of endoscopically diagnosed ulcers of rofecoxib compared to ibuprofen in a 12-week endoscopy trial in OA patients (RR=0.2). Table A1 also presents the RR of endoscopically diagnosed ulcers of rofecoxib and concomitant low-dose aspirin compared to ibuprofen in a 12-week endoscopy trial in OA patients (RR=0.9). Therefore, in similar endoscopy trials, the concomitant use of low-dose aspirin (81 mg/day) was associated with an elimination of the reduction of the risk of endoscopically diagnosed ulcers.

Table A1: Endoscopy trial of rofecoxib in OA patients without concomitant aspirin vs. endoscopy trial of rofecoxib in OA patients with concomitant aspirin

Treatment Group	Endoscopically diagnosed Ulcers	Incidence of Endoscopically diagnosed Ulcers	Comparison	RR	95% CI
Endoscopy Trial in OA Patients (12 Week Data) Without Aspirin[1]					
Placebo (n=182)	9	5%	—	—	
Rofecoxib 25 mg/day (n=187)	10	5%	rofecoxib — ibuprofen	0.2	**0.1, 0.4**
Rofecoxib 50 mg/day (n=182)	16	9%	—	—	
Ibuprofen 800 mg TID (n=187)	55	29%	—	—	
Endoscopy Trial in OA Patients (12-Weeks) With & Without Aspirin[2]					
Placebo (n=381)	21	6%	—	—	
ASA 81 mg/day (n=387)	27	7%	—	—	
Rofecoxib 25 mg/day & ASA 81 mg (n=377)	58	16%	rofecoxib/ASA81— ibuprofen	0.9	**0.7, 1.3**
Ibuprofen 800 mg TID (n=374)	62	17%	—	—	

[1] Rofecoxib label and Hawkey C. *Arthritis Rheum* 2000;43(2):370-377.
[2] Rofecoxib label and Laine L. *Gastroenterology* 2004:395-402.

Table A2 displays the results of 2 seven-day endoscopy trials in healthy subjects. In the first trial, the RR of endoscopically diagnosed ulcers of celecoxib and 81 mg of aspirin/day was lower than the RR of endoscopically diagnosed ulcers of the naproxen and 81 mg of aspirin/day group (RR = 0.3). In the second trial, the RR of endoscopically diagnosed ulcers of celecoxib and a higher dose of aspirin (325 mg/day) compared to the RR of endoscopically diagnosed ulcers of the naproxen and 325 mg of aspirin/day was lower (RR = 0.7). Higher aspirin doses are associated with reduction of the risk reduction of endoscopically diagnosed ulcers of a COX-2 inhibitor compared to a non-selective NSAID.

Table A2: Endoscopy trials of celecoxib in healthy subjects by concomitant aspirin dose (81 vs. 325 mg)

Treatment Group	Endoscopically diagnosed Ulcers	Incidence of Endoscopically diagnosed Ulcers	Comparison	RR	95% CI
Endoscopy Trial in Healthy Subjects With and Without Aspirin 81 mg/day[1,2]					
ASA 81 mg/day (n=129)	2	2%	–	–	
Celecoxib 200 mg & ASA 81 mg once daily (n=257)	18	7%	Celecoxib/ASA81 – Naproxen/ASA81	0.3	**0.2, 0.5**
Naproxen 500 mg BID & ASA 81 mg/day (n=257)	65	25%	–	–	
Endoscopy Trial in Healthy Subjects With and Without Aspirin 325 mg/day[1,3]					
ASA 325 mg/day (n=92)	7	8%	–	–	
Celecoxib 200 mg & ASA 325 mg once daily (n=182)	34	19%	Celecoxib/ASA325 – Naproxen/ASA325	0.7	**0.5, 1.0**
Naproxen 500 mg BID & ASA 325 mg/day (n=176)	48	27%	–	–	

[1] Upper endoscopies were performed at baseline and Day 7.
[2] Goldstein et al. *Dig Dis Sci* 2008:53;647-656.
[3] Goldstein et al. *Aliment Pharmacol Ther* 2006:23;1489-1498

11.2. Appendix – Effect of Aspirin on UGICs in CLASS

Table A3 displays UGICs in CLASS by concomitant low-dose aspirin use. In the non-aspirin subgroup, celecoxib reduced the risk of UGICs compared to the non-selective NSAIDs; however, in the concomitant low-dose aspirin group the risk of UGICs was similar in the celecoxib and non-selective NSAID groups. The use of concomitant low-dose aspirin in CLASS eliminated the treatment benefit of celecoxib.

Table A3: UGICs in CLASS by ASA use

Treatment Group	UGICs	UGICs per 100 pt-years	Comparison	RR	95% CI
Non-ASA Subgroup					
Celecoxib 400 mg BID (n=3105)	**8**	**0.4**	**Celecoxib-NSAID**	**0.6**	**0.2, 1.4**
Diclofenac 75 mg BID & Ibuprofen 800 mg BID (n=3124)	**14**	**0.8**	–	–	

ASA Subgroup					
Celecoxib 400 mg BID (n=882)	**9**	**1.7**	**Celecoxib-NSAID**	**1.3**	**0.5, 3.5**
Diclofenac 75 mg BID & Ibuprofen 800 mg BID (n=887)	**7**	**1.4**	**–**	**–**	

11.3. Appendix – COX-2 Inhibitor Outcome Trials

Table A4 displays the risk factors for NSAID-associated UGI Toxicity in the 4 outcome trials of COX-2 selective NSAIDs. In general the trials had similar risk factors except the concomitant use of low-dose aspirin differed in the trials. Additionally, the allowed dose of concomitant aspirin differed.

Table A4: Risk factors for UGI toxicity in the 4 COX-2 inhibitor outcome trials[1]

Outcome Trial	Treatment Groups	Mean Age	Prior UGIC	Prior UGI Symptomatic Event	Concurrent Low-dose ASA use[2]	Population
CLASS	celecoxib 400 mg BID, n=3987 diclofenac 75 mg BID, n=1996 ibuprofen 800 mg TID, n=1985	60 years	2%	8%	21%	72% OA, 28% RA
VIGOR	rofecoxib 50 mg/day, n=4047 naproxen 500 mg BID, n=4029	58 years	3%	8%	0%	100% RA
TARGET	lumiracoxib 400 mg/day, n=9117 ibuprofen 800 mg TID, n=4397 naproxen 500 mg BID, n=4730	63 years	0.3%	3%	24%	100% OA
MEDAL Program[3]	etoricoxib 60 or 90 mg/day, n=17,412 diclofenac 150 mg/day, n=17,289	63 years	N/A	7%	35%	72% OA, 28% RA

[1] These risk factors were well-balanced across all the treatment groups in all 4 trials

[2] In CLASS, low dose aspirin (≤ 325 mg/day) was allowed. In VIGOR, low-dose aspirin was not allowed. In TARGET, low dose aspirin (75 to 100 mg/day) was allowed. In the MEDAL program, low dose aspirin (≤ 100 mg/day was strongly encouraged for patients with cardiovascular, cerebral vascular, or peripheral vascular disease or diabetes. In the MEDAL program, 39% of the patients received PPIs in the treatment period.

[3] In the MEDAL Program, the diclofenac dose was either 75 mg BID or 50 mg TID

Table A5 displays the types of UGICs in each the 4 outcome trials of COX-2 selective NSAIDs. The majority of UGICs were due to serious bleeding from GUs and/or DUs. In the trials, the cause of the UGIC was not found or due to non-ulcer etiologies from 8% to 19% of the time.

Table A5: Types of UGICs in all treatment groups in the 4 COX-2 inhibitor outcome trials

	CLASS	VIGOR	TARGET	MEDAL
Total UGICs[1], N, (%)	**38 (100%)**	**53 (100%)**	**112 (100%)**	**160 (100%)**
Ulcer-related, n (%)	**35 (92%)**	**43 (81%)**	**N/A**	**131 (82%)**
Gastric ulcer bleed, n	**18**	**21**	**N/A**	**66**
Duodenal ulcer bleed, n	**13**	**14**	**N/A**	**40**
Gastric and/or duodenal ulcer, n	**1**	**1**	**N/A**	**9**
Gastric or duodenal perforation, n	**1**	**7**	**3**	**16**
Gastric outlet obstruction, n	**2**	**1**	**1**	**4**
Not ulcer-related or cause not found[2], n (%)	**3 (8%)**	**10 (19%)**	**N/A**	**29 (18%)**

[1] Total UGICs include all UGIC in the entire trial (including all treatment groups).

[2] Non-ulcer related includes esophageal, gastric, duodenal erosions or no lesion could be identified because stomach full of blood.

11.4. Appendix – Endoscopy trials of COX-2 selective NSAIDs and non-selective NSAIDs

Table A6 displays the 19 endoscopy trials of selective and non-selective NSAIDs obtained through a search of the literature, NDAs, and AC meetings. These 19 trials were obtained from the search of R, DB, active-controlled endoscopy trials of COX-2 selective NSAIDs or nonselective NSAIDs at least 12 weeks in arthritis patients anticipated requiring chronic NSAIDs. In all trials, patients had to have a baseline endoscopy that demonstrated no GUs or DUs and the primary endpoint was the cumulative incidence of patients who had an endoscopically diagnosed ulcer ≥ 3 mm in diameter and perceptible depth. The yellow highlighted trials were the 5 endoscopy trials that were selected for the cross-study comparisons.

Table A6: 19 endoscopy trials of COX-2 selective NSAIDs or non-selective NSAIDs

Endoscopy Trial		Comparators	Duration (weeks)	Reasons for exclusion[1]
diclofenac				
1	Roth et al 1995[2]	naproxen	12	no comparator
celecoxib				
2	N49-98-06-071	diclofenac, ibuprofen	12	N/A
3	N49-96-02-022	naproxen, placebo	12	no comparator
4	N49-98-06-021	naproxen, placebo	12	no comparator
5	N49-97-02-062	naproxen	12	no comparator
6	I49-96-02-041	diclofenac	24	no baseline EGD
7	I49-00-07-849	diclofenac	12	different dose[4]
rofecoxib				
8	098C[5]	naproxen, placebo	12	N/A
9	044	ibuprofen, placebo	24	no comparator
10	045	ibuprofen, placebo	24	no comparator
11	Laine 2004[6]	ibuprofen, aspirin 81 mg, placebo	12	no comparator
valdecoxib				
12	N91-00-26-048[7]	diclofenac, ibuprofen, placebo	12	N/A
13	N91-00-06-053	diclofenac	26	no comparator
14	Kivitz et al 2002[8]	naproxen, placebo	12	no comparator
15	N91-00-06-047	naproxen	26	no comparator
lumiracoxib				
16	CCOX189-0110[9]	celecoxib, ibuprofen	13	N/A
17	CCOX189-0126[10]	celecoxib, ibuprofen	13	N/A
etoricoxib				
18	029	ibuprofen, placebo	12	no comparator
19	026	naproxen, placebo	12	no comparator

[1] No comparator = trials that did not have two NSAIDs that were identical as an outcome trial.
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Table A7 displays the risk factors for NSAID-associated UGI toxicity in the 5 selected endoscopy trials of selective and non-selective NSAIDs. The incidence of prior UGI symptomatic events and concomitant low-dose aspirin use were slightly different in the trials.

Table A7: Risk factors for UGI toxicity in the 5 selected COX-2 inhibitor endoscopy trials

EGD Trial (Study #)	Treatment Groups[1]	Mean Age (population)	Prior UGI Symptomatic Event	Prior UGIC	Concurrent ASA Use	Baseline Positive *H. pylori*[2]
celecoxib-1 (N49-98-06-071)	**celecoxib 200 mg BID, n=356 diclofenac 75 mg BID, n=372 ibuprofen 800 mg TID, n=334**	**57 years (OA, RA)**	**12%**	**2%**	**12%**	**31%**
rofecoxib-1 (098C)	**rofecoxib 50 mg, n=211 naproxen 500 mg BID, n=210 placebo, n=212**	**52 years (RA)**	**12%**	**N/A**	**1%**	**60%**
valdeocoxib-1 (N91-00-26-048)	**diclofenac 75 mg BID, n=187 ibuprofen 800 mg TID, n=184 valdecoxib 10 mg, n=189 valdecoxib 20 mg, n=198 placebo, n=178**	**60 years (OA)**	**13%**	**N/A**	**15%**	**39%**
lumiracoxib-1 (CCOX189-0110)	**lumiracoxib 400 mg q d, n=212 lumiracoxib 800 mg q d, n=207 celecoxib 200 mg BID, n=213 ibuprofen 800 mg TID, n=199**	**52 years (RA)**	**6%**	**0%**	**1%**	**44%**

lumiracoxib-2 (CCOX189-0126)	**lumiracoxib 400 mg q d, n=253 lumiracoxib 200 mg q d, n=257 celecoxib 200 mg q d, n=253 ibuprofen 800 mg TID, n=248**	**58 years (OA)**	**6%**	**0%**	**4%**	**71%**

[1] endoscopy evaluable all treated patients who had at least one post-baseline EGD
[2] Patients were allowed to participate in these trials if they were *H. pylori* negative or positive at baseline.

11.5. Appendix – Comparisons of Endoscopy Trials with Outcome Trials

Identical NSAID dosing regimens (i.e., ibuprofen, diclofenac, naproxen, rofecoxib, and lumiracoxib)

Tables A8, A9, A10, and A11 compare the RR of endoscopically diagnosed ulcers in endoscopy trials with the RR of UGICs in outcome trial by concomitant low-dose aspirin use (low vs. high).

Table A8: Diclofenac compared to ibuprofen - RR of endoscopically diagnosed ulcers in Study Valdecoxib-1 to the RR of UGICs in CLASS

Valdecoxib-1 Endoscopy Trial (15% aspirin use)				
Treatment Groups	**Endoscopically diagnosed Ulcers**	**Incidence of Endoscopically diagnosed Ulcers**	**Comparison**	**RR**
Diclofenac 75 mg BID (n=187)	25	13%	Diclofenac – Ibuprofen	1.0
Ibuprofen 800 mg TID (n=184)	25	14%	–	–
Valdecoxib 10 mg/day (n=189)	7	4%	–	–
Valdecoxib 20 mg/day (n=198)	7	4%	–	–
Placebo (n=178)	8	5%	–	–
CLASS (21% aspirin use)				
Treatment Group	**UGICs**	**UGICs/100 pt-years**	**Comparison**	**RR**
Celecoxib 400 mg BID (n=3,987)	17	0.7	–	–
Diclofenac 75 mg BID (n=1,996)	10	0.9	Diclofenac – Ibuprofen	0.9
Ibuprofen 800 mg TID (n=1,985)	11	1.0	–	–

Table A9: Rofecoxib compared to naproxen - RR of endoscopically diagnosed ulcers in Study Rofecoxib-1 to the RR of UGICs in VIGOR

Rofecoxib-1 Endoscopy Trial (1% Aspirin Use)				
Treatment Groups	**Endoscopically diagnosed Ulcers**	**Incidence of Endoscopically diagnosedUlcers**	**Comparison**	**RR**
Rofecoxib 50 mg/day (n=211)	**14**	**7%**	**Rofecoxib – Naproxen**	**0.3**
Naproxen 500 mg BID (n=210)	**51**	**26%**	–	–
Placebo (n=212)	**6**	**3%**	–	–
VIGOR (No Aspirin Use)				
Treatment Group	**UGICs**	**UGICs/ 100 pt-years**	**Comparison**	**RR**
Rofecoxib 50 mg/day (n=4,047)	**16**	**0.6**	**Rofecoxib – Naproxen**	**0.4**
Naproxen 500 mg BID (n=4,029)	**37**	**1.4**	–	–

Table A10: Lumiracoxib compared to ibuprofen - RR of endoscopically diagnosed ulcers in Study Lumiracoxib-1 to the RR of UGICs in non-aspirin subgroup in TARGET

Treatment Groups	**Endoscopically diagnosed Ulcers**	**Incidence of Endoscopically diagnosed Ulcers**	**Comparison**	**RR**
Lumiracoxib-1 Endoscopy Trial (1% Aspirin Use)				
Lumiracoxib 400 mg/day (n=212)	6	3%	Lumiracoxib – Ibuprofen	0.2
Lumiracoxib 800 mg/day (n=207)	9	4%	–	–
Celecoxib 200 mg BID (n=213)	4	2%	–	–
Ibuprofen 800 mg TID (n=199)	27	14%	–	–
TARGET (Non-Aspirin Subgroup)				
Treatment Group	**UGICs**	**UGICs/ 100 pt-years**	**Comparison**	**RR**
Lumiracoxib 400 mg/day (n=6,950)	14	0.3	Lumiracoxib - Ibuprofen	0.3
Ibuprofen 800 mg TID n=3,431)	28	1.1	–	–
Naproxen 500 mg BID (n=3,537)	36	1.4	–	–

Table A11: Lumiracoxib compared to ibuprofen - RR of endoscopically diagnosed ulcers in Study Lumiracoxib-2 to the RR of UGICs in non-aspirin subgroup in TARGET

Treatment Groups	Endoscopically diagnosed Ulcers	Incidence of Endoscopically diagnosed Ulcers	Comparison	RR
Lumiracoxib-2 Endoscopy Trial (4% Aspirin Use)				
Lumiracoxib 200 mg/day (n=257)	11	4%	–	–
Lumiracoxib 400 mg/day (n=253)	10	4%	Lumiracoxib – Ibuprofen	0.3
Celecoxib 200 mg q day (n=253)	8	3%	–	–
Ibuprofen 800 mg TID (n=248)	39	16%	–	–
TARGET (Non-Aspirin Subgroup)				
Treatment Group	**UGICs**	**UGICs/ 100 pt-years**	**Comparison**	**RR**
Lumiracoxib 400 mg/day (n=6,950)	14	0.3	Lumiracoxib – Ibuprofen	0.3
Ibuprofen 800 mg TID (n=3,431)	28	1.1	–	–
Naproxen 500 mg BID (n=3,537)	36	1.4	–	–

Identical ibuprofen and diclofenac dosing regimens, but different celecoxib dosing regimen

Tables A12, A13, and A14 compare the RR of endoscopically diagnosed ulcers in endoscopy trials with the RR of UGICs in outcome trial by concomitant low-dose aspirin use (low vs. high).

Table A12: Celecoxib compared to ibuprofen - RR of endoscopically diagnosed ulcers in Study Celecoxib-1 to the RR of UGICs in CLASS

Celecoxib-1 Endoscopy Trial (12% aspirin use)				
Treatment Groups	**Endoscopically diagnosed Ulcers**	**Incidence of Endoscopically diagnosed Ulcers**	**Comparison**	**RR**
Celecoxib 200 mg BID (n=356)	25	7%	Celecoxib─ Ibuprofen	0.3
Diclofenac 75 mg BID (n=372)	36	10%	─	─
Ibuprofen 800 mg TID (n=334)	78	23%	─	─
CLASS (21% aspirin use)				
Treatment Group	**UGICs**	**UGICs/100 pt-years**	**Comparison**	**RR**
Celecoxib 400 mg BID (n=3,987)	17	0.7	Celecoxib ─ Ibuprofen	0.8
Diclofenac 75 mg BID (n=1,996)	10	0.9	─	─
Ibuprofen 800 mg TID (n=1,985)	11	1.0	─	─

Table A13: Celecoxib compared to ibuprofen - RR of endoscopically diagnosed ulcers in Study Lumiracoxib-1 to the RR of UGICs in the non-aspirin subgroup in CLASS

Lumiracoxib-1 Endoscopy Trial (1% Aspirin Use)				
Treatment Groups	**Endoscopically diagnosed Ulcers**	**Incidence of Endoscopically diagnosed Ulcers**	**Comparison**	**RR**
Lumiracoxib 400 mg/day (n=212)	6	3%	─	─
Lumiracoxib 800 mg/day (n=207)	9	4%	─	─
Celecoxib 200 mg BID (n=213)	4	2%	Celecoxib ─ Ibuprofen	0.1
Ibuprofen 800 mg TID (n=199)	27	14%	─	─
CLASS (Non-Aspirin Subgroup)				
Treatment Group	**UGICs**	**UGICs/ 100 pt-years**	**Comparison**	**RR**
Celecoxib 400 mg BID (n=3,105)	8	0.4	Celecoxib ─ Ibuprofen	0.4
Diclofenac 75 mg BID (n=1,551)	4	0.5	─	─
Ibuprofen 800 mg TID (n=1,573)	10	1.1	─	─

Table A14: Celecoxib compared to diclofenac - RR of endoscopically diagnosed ulcers in Study Celecoxib-1 to the RR of UGICs in CLASS

Celecoxib-1 Endoscopy Trial (12% aspirin use)				
Treatment Groups	**Endoscopically diagnosed Ulcers**	**Incidence of Endoscopically diagnosed Ulcers**	**Comparison**	**RR**
Celecoxib 200 mg BID (n=356)	25	7%	Celecoxib ─ Diclofenac	0.7
Diclofenac 75 mg BID (n=372)	36	10%	─	─
Ibuprofen 800 mg TID (n=334)	78	23%	─	─
CLASS (21% aspirin use)				
Treatment Group	**UGICs**	**UGICs/100 pt-years**	**Comparison**	**RR**
Celecoxib 400 mg BID (n=3,987)	17	0.7	Celecoxib ─ Diclofenac	0.9
Diclofenac 75 mg BID (n=1,996)	10	0.9	─	─
Ibuprofen 800 mg TID (n=1,985)	11	1.0	─	─