Response to Article by Juni *et al.* Published in *The Lancet* on Nov. 5

In an article that appeared in Lancet on Nov. 5, 2004, Juni *et al.* present a meta-analysis of rofecoxib data and conclude that an increased risk for cardiovascular events on rofecoxib was apparent in the year 2000. These conclusions are based on an analysis that violates the basic principle of meta-analyses to combine "like with like". In this analysis, the authors combined data from studies with 3 different kinds of comparators. The conclusion by Juni *et al.* of a difference in myocardial infarction (MI) risk for rofecoxib regardless of comparator is driven by the difference between rofecoxib and a single comparator, naproxen, especially by the results of VIGOR (Bombardier C, *et al. N Engl J Med* 2000; **343:** 1520–28). The data in this article had already been included in the first rofecoxib pooled analysis published in 2001 by Konstam *et al.* (*Circulation* 2001;104:2280) and again in 2003 (*Am Heart J* 2003;146:591). These pooled analyses demonstrated a difference in cardiovascular risk between rofecoxib and naproxen but not between rofecoxib and non-naproxen NSAIDs or placebo.

Juni *et al.* combined data from a subset of VIOXX studies analyzed by Konstam *et al.* Juni *et al.* conclude that, until mid 2000, there was no evidence of a difference in the relative risk of an MI on VIOXX compared to other drugs but that, starting in 2000, there was a difference. Careful review of their analysis reveals that studies published before 2000 compared rofecoxib to either placebo or to the non-naproxen NSAIDs ibuprofen, diclofenac, or nabumetone (Table 1). The study in 2000 that accounted for the difference noted by the authors was VIGOR, preliminary results of which first became available and were immediately disclosed in March 2000, were then published in November, and received wide attention. The final data were provided to the FDA in the fall of 2000 and published on the FDA's website in February, 2001. After VIGOR, the majority of the patient data in studies cited by the authors continued to involve comparisons of VIOXX with naproxen (Table 1).

The authors' analysis by comparator confirms that the only statistically significant difference in MI risk was between rofecoxib and naproxen, not between rofecoxib and either placebo or non-naproxen NSAIDs. The authors justify combining the data across the comparators because confidence intervals against individual comparators were wide and the statistical test for interaction was not significant. This use of an underpowered statistical test as the sole justification for combining the data is scientifically inappropriate and fails the requirement to combine "like with like"; there are known different biologic effects of the comparators on platelet function and the data demonstrate large differences in relative risk between the comparator groups (Table 2). In a complete analysis of the individual patient data using Cox proportional hazards regression, a more statistically powerful technique, Konstam *et al.* found substantial heterogeneity between naproxen-controlled studies and other studies, validating the appropriateness of segregating naproxen-controlled data (Table 2). The inappropriate combining of heterogeneous data by Juni *et al.* invalidates the results and conclusions of their meta-analysis.

In addition, Juni *et al.* did not use all available data, notably the large placebo-controlled Alzheimer's Disease studies comparing rofecoxib to placebo. Cardiovascular data from

these studies were included in the US labeling for rofecoxib. The MI data are available on the FDA website at http://www.fda.gov/ohrms/dockets/ac/01/briefing/3677b2_01_merck.pdf. There were 9 MIs on rofecoxib and 12 on placebo out of more than 2000 patients treated for approximately 1 year. There is no scientific reason to exclude these data as there is no basis for a difference in MI risk between Alzheimer's Disease patients and other patients included, such as osteoarthritis or chronic low back pain patients. This selective omission of a large placebo-controlled dataset available in 2001 after VIGOR and which showed no difference between rofecoxib and placebo limits the authors' conclusions.

The authors consider possible differences between their analysis and previously cited rofecoxib pooled analyses. They claim that use of a combined endpoint could obscure findings restricted to one of its components. Examination of the data in Konstam *et al.* show that this is not the case; there is consistency between the APTC combined endpoint and MI (see table 6 in Konstam *et al.*). Indeed, the principle difference between Juni *et al.* and the other rofecoxib combined analyses is not in the endpoint but in the inappropriate pooling of comparators by Juni *et al.* as noted above. The authors also claim that the relative risk between rofecoxib and comparators was the same in studies =6 months and <6 months. However, as with the meta-analysis of all trials, this result is confounded by comparator.

In summary, the data contained in the meta-analysis by Juni *et al.* had been previously disclosed and analyzed. As in the pooled analyses of randomized rofecoxib controlled clinical trials published in 2001 and again in 2003, the Juni *et al.* meta-analysis shows no significant difference with rofecoxib versus placebo, no significant difference with rofecoxib versus non-naproxen NSAIDs and a significantly lower risk with naproxen versus rofecoxib. However, Juni *et al.* went on to combine all the data in a scientifically inappropriate manner, counter to basic principles of meta-analysis. All their conclusions for a signal beginning in 2000 were driven by the comparison to naproxen, largely by VIGOR. Prior to APPROVe, in placebo- and non-naproxen NSAID-controlled studies, the data did not support an increased risk of cardiovascular events with rofecoxib. In the APPROVe trial, for the first time, there was an increased risk of confirmed cardiovascular events beginning after 18 months of treatment in patients taking rofecoxib compared to those taking placebo. Within one week of learning those results, Merck acted in what it believed was the best interest of patients and voluntarily withdrew VIOXX from the market.

Table 1
Sequence of Studies and Comparator Usage in Juni *et al*. Figure 3

Protocol Number	Comparators	Year
029	Placebo	1997
029 extension	Diclofenac	1998
035	Diclofenac	1998
040	Placebo, Ibuprofen	1998
045	Placebo, Ibuprofen	1998
058	Placebo, Nabumetone	1998
034	Diclofenac	1999
085	Placebo, Nabumetone	1999
068 ext	**Naproxen**	2000
088, 089 (VIGOR)	**Naproxen**	2000
090	Placebo, Nabumetone	2000
096	**Placebo, Naproxen**	2000
102 (ADVANTAGE)	**Naproxen**	2000
096 ext	**Naproxen**	2001
097 ext	**Naproxen**	2001
120, 121	Placebo	2001

Table 2
Relative Risk of Cardiovascular Events in Published Pooled and Meta-Analyses

	Konstam *et al*., 2001	Reicin *et al*., 2002	Weir *et al*., 2003	Juli *et al*., 2004
Endpoint	APTC	Investigator reported CV thrombotic event	APTC	MI
Placebo	0.84 (0.51, 1.38)	0.94 (0.31, 2.92)	0.93 (0.57, 1.53)	1.04 (0.34, 3.12)
Non-naproxen NSAIDs	0.79 (0.40, 1.55)	1.04 (0.49, 2.21)	0.84 (0.45, 1.63)	1.55 (0.55, 4.36)
Naproxen	1.69 (1.07, 2.69)		1.69 (1.07, 2.69)	2.93 (1.36, 6.33)
	MI=myocardial infarction			
	APTC=Non-fatal cardiac, non-fatal and total CV, hemorrhagic, and unknown deaths			
	Investigator-reported cardiovascular events=Coronary artery disease, MI, unstable angina, cerebrovascular accident, transient ischemic attack, deep venous thrombosis			