Preliminary Review of APPROVe data –
Background package for February, 2005 AC meeting.

IND 46,894 – Vioxx
Sponsor: Merck

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***1. Background**:*

Merck withdrew Vioxx from the market on September 30, 2004, upon the ESMB (external safety monitoring board), review of the interim analysis of study 122, also known as APPROVe. The full name of this protocol is: "A multicenter, randomized, parallel-group, placebo-controlled, double blind study to determine the effect of 156 weeks of treatment with MK-0966 on the recurrence of neoplastic polyps of the large bowel in patients with a history of colorectal adenomas"). Preliminary analyses from APPROVe were presented to FDA on September 28, 2004. The cut-off date for these analyses was 8/16/04. The final report from APPROVe has not been submitted to FDA.

2. Results of APPROVe as presented to FDA on September 28, 2004

APPROVe compared Rofecoxib 25mg vs. *Placebo in approximately 2600 patients with a history of colonic polyps. It had a 3-Year on-drug Treatment Period with a one-year follow up period. Colonoscopies were done at screening, 1 year and 3 years on-drug, with a follow up colonoscopy at year 4 (1 year off-therapy) to assess rebound. The mean age of patients was 59 years (30% >65 years) and 60% were male. Of note, 15% were taking low dose aspirin for cardiovascular prophylaxis. The study had an ESMB that met regularly every 6 months. Cardiovascular adverse events were referred to an independent CV adjudication committee that evaluated the cases in a blinded manner. At the September 17, 2004 ESMB meeting, based on the imbalance in the number of cardiovascular thrombotic events, the ESMB recommended stopping the trial (Tables 1 2 and 3). The definition of confirmed APTC (Anti-Platelet Trialists Collaboration) events and CV/T (cardiovascular thrombotic events) are the same as used in prior Merck trials: APTC includes cardiovascular deaths, non-fatal myocardial infarction and non fatal stroke; CV/T includes APTC events plus unstable angina, transient ischemic attack and peripheral events, while excludes hemorrhagic strokes.*

Table 1. Confirmed CV thrombotic events in APPROVe

	Placebo (N=1299)		Rofecoxib (N=1287)	
	3315 Patient-Years		3041 Patient-Years	
	n(%)†	Rate‡	n(%)†	Rate‡
Cardiac Events	**11(0.85)**	**0.33**	**30(2.33)**	**0.99**
Acute myocardial infarction	8(0.62)	0.24	20(1.55)	0.66
Fatal acute myocardial infarction	3(0.23)	0.09	1(0.08)	0.03
Sudden cardiac death	1(0.08)	0.03	3(0.23)	0.10
Unstable angina pectoris	4(0.31)	0.12	7(0.54)	0.23
Cerebrovascular Events	**7(0.54)**	**0.21**	**15(1.17)**	**0.49**
Fatal ischemic cerebrovascular stroke	0(0.00)	0.00	0(0.00)	0.00
Ischemic cerebrovascular stroke	6(0.46)	0.18	11(0.85)	0.36
Transient ischemic attack	2(0.15)	0.06	5(0.39)	0.16
Peripheral Vascular Events	**7(0.54)**	**0.21**	**3(0.23)**	**0.10**
Peripheral arterial thrombosis	1(0.08)	0.03	1(0.08)	0.03
Peripheral venous thrombosis	4(0.31)	0.12	2(0.16)	0.07
Pulmonary embolism	2(0.15)	0.06	0(0.00)	0.00
Total number of patients with endpoint	**25(1.92)**	**0.75**	**45(3.50)**	**1.48**

Table 2. Confirmed CV/thrombotic endpoints by aspirin use

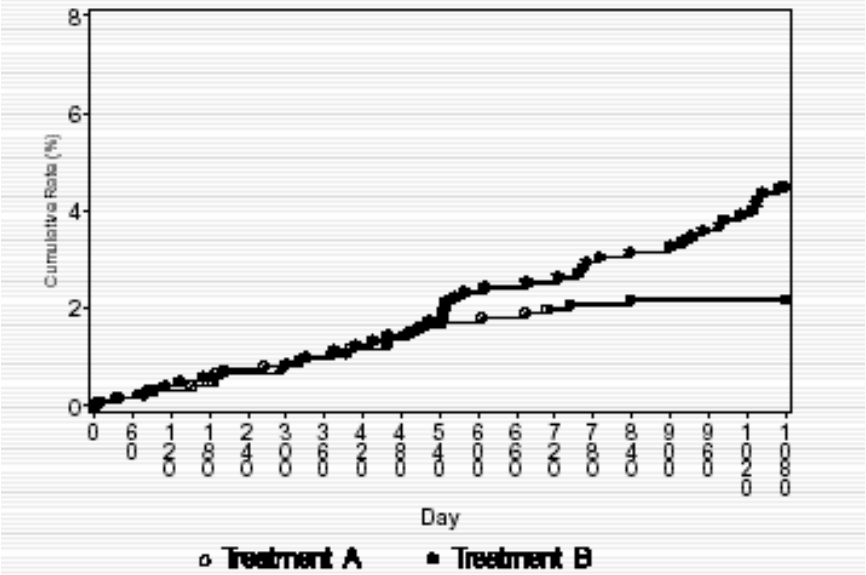
	Rofecoxib n/PYR (rate)	Placebo n/PYR (rate)	RR, p-value (95% CI)
All patients	45/3041 (1.48) N=1287	25/3315 (0.75) N=1299	1.96 p=0.007
ASA users	10/485 (2.06) N=213	5/504 (0.99) N=204	2.04 (0.70, 5.96)
Non-ASA users	35/2557 (1.37) N=1074	20/2811 (0.71) N=1095	1.93 (1.11, 3.34)

Table 3. APTC composite endpoints by aspirin use

	Rofecoxib n/PYR (rate)	Placebo n/PYR (rate)	RR, p-value (95% CI)
All patients	33/3053 (1.08) N=1287	16/3322 (0.48) N=1299	2.25 p=0.008
ASA users	5/489 (1.02) N=213	4/505 (0.79) N=204	1.29 (0.28, 6.50)
Non-ASA users	28/2564 (1.09) N=1074	12/2817 (0.43) N=1095	2.57 (1.31,5.06)

It is unclear why the denominator is different for Tables 2 and 3. Clarification is pending.

Figure 1. Time to Event Plot. Confirmed CV/Thrombotic events in APPROVe



A- placebo; B- rofecoxib 25 mg

There was approximately twice the number of cardiovascular thrombotic events in patients receiving rofecoxib 25 mg as compared to placebo. Results were consistent in any way one looked at them: all investigator reported CV/T events (data not shown), confirmed CV/T events (Table 1 and 2) or APTC events (Table 3). As per Figure 1., the hazard ratio for CV/T events for rofecoxib and placebo increased after 18 months of exposure, however, it is unclear whether the rate in rofecoxib increased over time or the rate in placebo made a plateau. (Analyses of risk over time are pending at the time of this review.)

Reviewer's comments:

- These results are consistent with VIGOR (rofecoxib 50 mg as compared to naproxen) in the overall number of CV/T events (twice on rofecoxib), the number of cardiovascular deaths (no difference between groups) and the number of MI (an excess on rofecoxib as compared to the comparator), although in VIGOR the difference between rofecoxib and naproxen was observed much earlier (starting at approximately 6 weeks, with more marked separation after 6-8 months). It is unclear why this difference in risk between rofecoxib and naproxen occurs earlier. It might be related to a different mechanism or to the fact that rofecoxib was used at twice the dose used in APPROVe.

- The results are not consistent with those of the Alzheimer's studies (078 + 091) as presented in the March 30, 2004 submission to NDA 21-042), of rofecoxib 25 mg as compared to placebo for up to 36 months. In this database there was no difference in the number of total CV/T events and MI but there was half the number of cerebrovascular events in rofecoxib as compared to placebo. Of note,

in the Alzheimer's studies, total cause mortality and CV/T mortality were higher on rofecoxib as compared to placebo (see Medical Officer review dated 12/18/04). Information on total cause mortality in APPROVe is not available at present.

- The rate of CV events is different in different studies. For instance, the percentage of MI was 0.5 and 0.1% for rofecoxib 50 mg and naproxen, respectively in VIGOR (in patients with RA); it was 1.3 and 1.3 % on rofecoxib 25 mg and placebo, respectively in the Alzheimer's studies and 1.6 and 0.6 % for rofecoxib 25 mg and placebo, respectively in APPROVe (patients with a history of colonic polyps). Different populations seem to have a different background rate of MI. These studies also had different duration and doses of rofecoxib. It is unclear which would be the best population to address CV issues with the selective and non-selective NSAIDs. Should these studies use placebo or naproxen as the active comparator? And what dose should be used (the highest dose recommended for chronic use or a higher dose)? What is clear from these data is that a study that would address CV safety needs to allow sufficiently long exposure, of at least 2 or 3 years.

- The mechanism for this excess in CV/T events on rofecoxib (and potentially for other selective and non-selective NSAIDs) is uncertain. There may be more than one mechanism, one of which could be the effect of rofecoxib on blood pressure (BP). Analyses of CV/T events in relationship to BP changes in APPROVe (see section 3.2 of this memo) have not demonstrated so far that that is the sole explanation for the findings.

- Of note, 3 shows that relative risk of APTC events is smaller in the subgroup of patients taking low dose aspirin as compared to those not taking low dose aspirin, although the risk is still higher for rofecoxib as compared to placebo (RR= 1.29). This observation is consistent with that of TARGET (lumiracoxib vs. naproxen and lumiracoxib vs. ibuprofen) and may be due to the fact that low dose aspirin might prevent cardiovascular thrombotic events. It is also possible that the number of patients is too small to detect differences in APTC events between groups.

  Some cardiologists have criticized FDA and suggested that a clinical trial to address cardiovascular issues with COX-2 selective agents should have been conducted in patients at high cardiovascular risk. However, such population with 100% use of low dose aspirin could potentially require huge number of patients in studies of longer duration in order to observe significant differences in cardiovascular events between treatment groups.

3. October 8, 2004 submission

Review of analyses of CV/T events in relation to BP changes in APPROVe.

The Sponsor conducted several analyses of CV/T events in relation to BP. Some of these analyses are included in this review. As seen in Table 4. CV/T events are more common among those patients with baseline blood pressure above DBP of 90 or SBP of 140 mmHg. However, the relative risk of CV/T events for Vioxx as compared to placebo, is consistently elevated among those patients with normal and even low baseline blood pressure (RR = 1.5 to 3.5).

Table 4. Patients with investigator reported thromboembolic or APTC events (excluding non-CV deaths) by baseline BP in APPROVe.

Baseline BP	*Placebo Events/patient years (rate x 100 pt years)*	*Rofecoxib 25 mg Events/patient years (rate x 100 pt years)*	*Relative risk*
	N= 1299	*N= 1287*	
DBP≥100 or SBP≥ 160	*5/189 (2.7)*	*7/176 (4.0)*	*1.524*
DPB 90-99 or SBP 140-159	*19/1026 (1.9)*	*26/846 (3.1)*	*1.660*
DBP 85-89 or SBP 130-139	*14/704 (2.0)*	*23/746 (3.1)*	*1.555*
DBP 80-84 or SBP 120-129	*4/808 (0.5)*	*12/705 (1.7)*	*3.433 (p<0.05)*
DBP <80 and SBP <120	*2/547 (0.4)*	*6/546 (1.1)*	*3.159*

(From Sponsor's Table 10.d. of October 8, 2004 submission).

Table 5. Patients with investigator reported thromboembolic or APTC events (excluding non CV deaths) by on-treatment Hypertension in APPROVe.

On treatment HTN	*Placebo Events/patient years (rate x 100 pt years)*	*Rofecoxib 25 mg Events/patient years (rate x 100 pt years)*
Patients without HTN	*32/2510 (1.3)*	*35/2058 (1.7)*
Patients with HTN (twice or more)	*8/381 (2.1)*	*18/520 (3.5)*

*n=events. * Hypertension defined as patients with DBP ≥ 100 or DBP ≥ 160 mm Hg twice or more. (From Sponsor's Table 11.d. of October 8, 2004 submission).*

Table 5 suggests that the rate of investigator reported CV/T or APTC events is greater among patients who had hypertension during the study (as defined by DBP ≥ 100 or DBP ≥ 160 mm Hg in two or more measurements) for both, the rofecoxib and placebo groups as compared to those who did not develop hypertension, and that more patients developed hypertension in the rofecoxib group as compared to placebo. However, the relative risk of CV/T events is greater in the rofecoxib group as compared to placebo, regardless of hypertension status.

Reviewer's comment: This observation suggests that while hypertension is important, there may be another mechanism to explain the different rate of CV/T events between rofecoxib and placebo in this study.

Another possibility is that increase in blood pressure, even if not as marked as DBP ≥ 100 or SBP ≥ 160 mm Hg may have an effect in increasing the risk of CV/T events. Data from the Framingham Heart Study suggest that even high-normal blood pressure is associated with an increased risk of cardiovascular disease.

Additional analyses in patients who develop borderline HTN (defined as DBP ≥ 90 or SBP ≥ 140 mm Hg) and in patients taking concomitant antihypertensive medications (by different categories of anti-hypertensive) are pending at the time of this review.