VIOXX CV UPDATE

Interim Data from APPROVe Study
thru 8/16/04

VIOXX Prespecified Analysis of CV Safety *vs.* Placebo

- Prospective combined analysis of 3 studies comparing rofecoxib 25mg *vs.* placebo
  - APPROVe: reduction in recurrent adenomatous colon polyps
  - ViP: decreased incidence of prostate cancer in at-risk patients
  - VICTOR: decreased colon cancer recurrence and increased survival (Oxford University Study)

APPROVe Study Design

- Rofecoxib 25mg *vs.* Placebo
- Approx. 2600 patients
- 3-Year On-Drug Treatment Period
- Colonoscopies
  - Screening, 1 yr, 3 yr
  - F/U at year 4 after withdrawal of therapy (assess rebound)
- FPI in 2000

APPROVe Baseline Characteristics

- Age
  - 59 mean (range 40 to 96)
  - 30% were >65 years
- 60% Male
- 15% low-dose aspirin users

APPROVe CV Events

- 118 investigator-reported events
  - 74 rofecoxib; 44 placebo
- 70 Confirmed thrombotic events
  - 45 rofecoxib; 25 placebo
- 49 APTC events
  - 33 rofecoxib; 16 placebo

APPROVe CV Events

	Rofecoxib N=1287 n/PYR (rate)	Placebo N=1299 n/PYR (rate)	RR p-value
Confirmed thrombotic	45/3041 (1.48)	25/3315 (0.75)	1.96 p=0.007
APTC	33/3053 (1.08)	16/3322 (0.48)	2.25 p=0.008

APPROVe Confirmed Thrombotic Events: ASA Subgroups

	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)

APPROVe APTC Events: ASA Subgroups

	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)

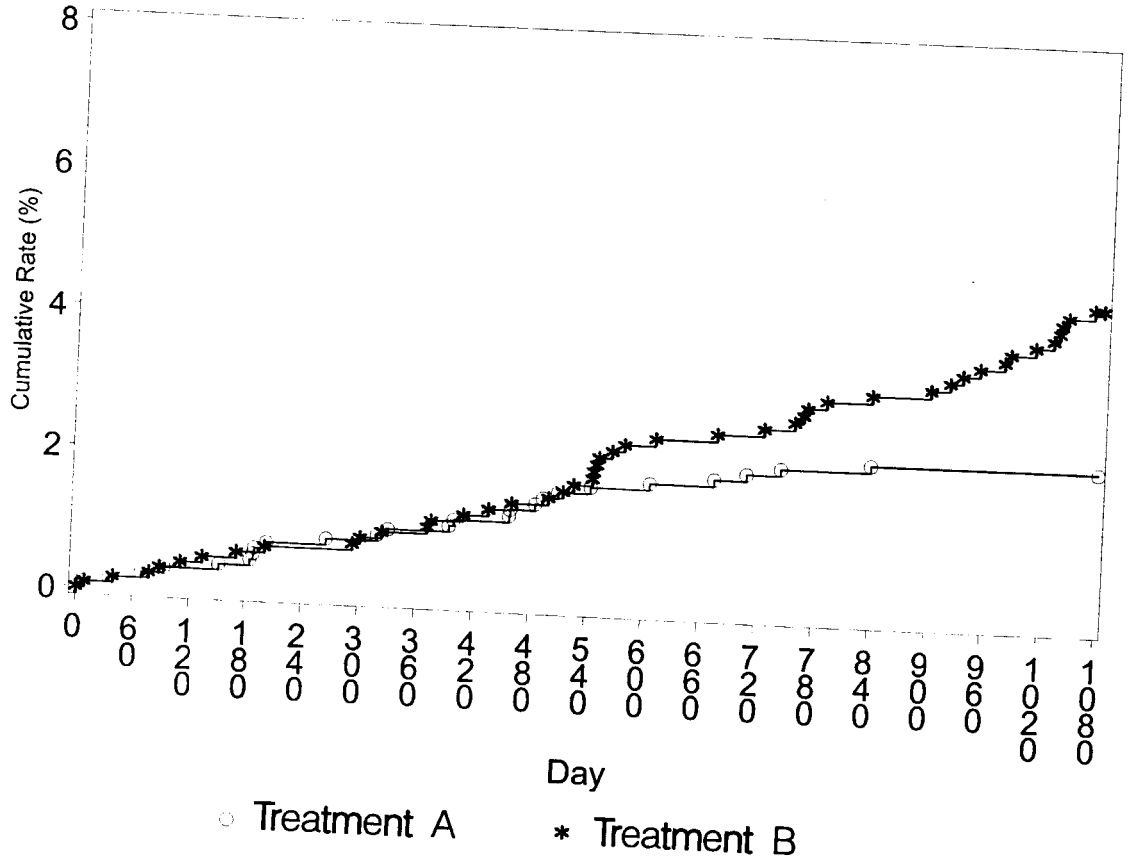
APPROVE Confirmed Thrombotic Endpoint

	Placebo (N=1299) 3315 Patient-Years		Rofecoxib (N=1287) 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**

APPROVe APTC Combined Endpoint

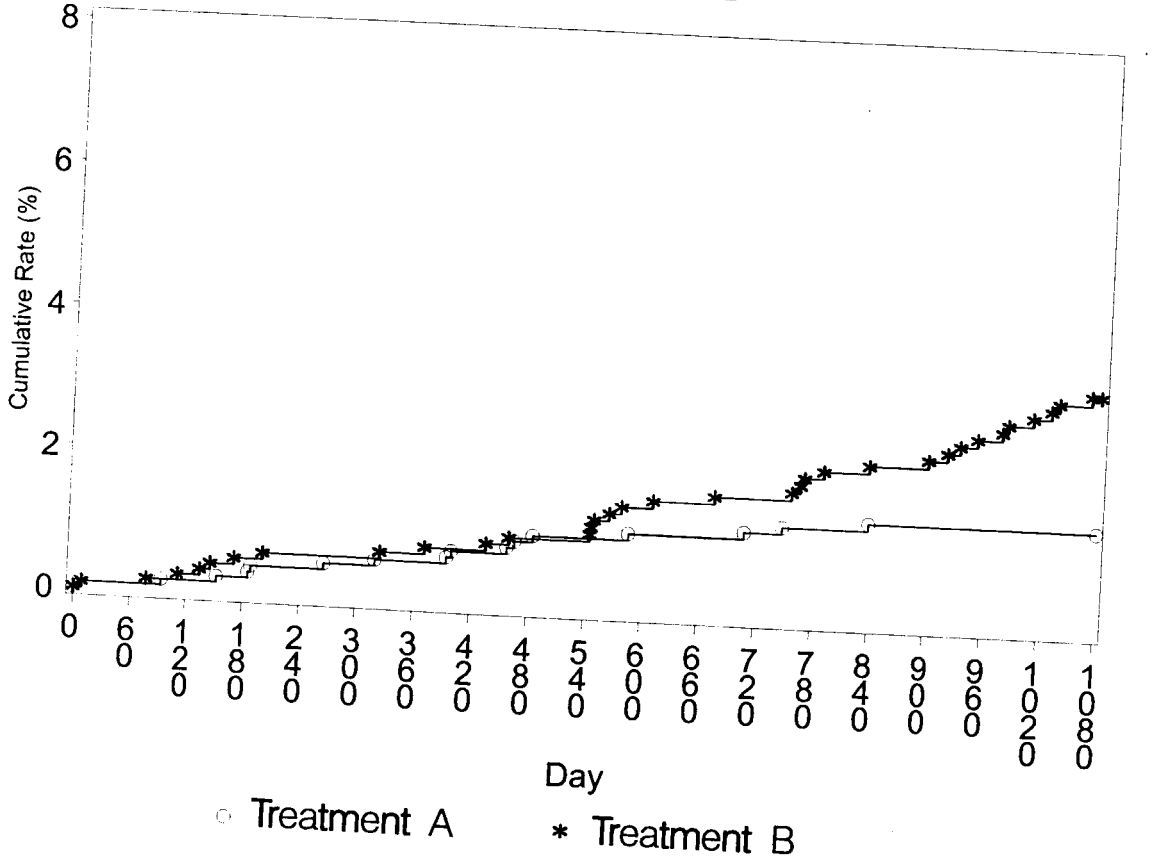
	Placebo (N=1299) 3322 Patient-Years		Rofecoxib (N=1287) 3053 Patient-Years	
	n(%)†	Rate‡	n(%)†	Rate‡
Cardiac Events	**9(0.69)**	**0.27**	**23(1.79)**	**0.75**
Acute myocardial infarction	8(0.62)	0.24	20(1.55)	0.66
Fatal acute myocardial infarction	3(0.23)	0.09	1(0.08)	0.03
Sudden cardiac death	1(0.08)	0.03	3(0.23)	0.10
Cerebrovascular Events	**6(0.46)**	**0.18**	**11(0.85)**	**0.36**
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
Hemorrhagic Events	**1(0.08)**	**0.03**	**1(0.08)**	**0.03**
Fatal hemorrhagic stroke	0(0.00)	0.00	0(0.00)	0.00
Hemorrhagic stroke	1(0.08)	0.03	1(0.08)	0.03
Total number of patients with endpoint	**16(1.23)**	**0.48**	**33(2.56)**	**1.08**

APPROVE Confirmed Thrombotic Endpoint



With adiudicated/confirmed thromboembolic serious AEs

APPROVe APTC Combined Endpoint



With APTC AEs

APPROVe Other Safety Info

- Blood Pressure
  - 4mm increase average SBP
  - 2mm increase average DBP
  - Significant increase in HTN-related AEs
- Significant increase in edema-related AEs
- Significant increase in CHF
- No mortality imbalance
  - 5 rofecoxib; 5 placebo

Additional Analyses Were Performed Including CV Events by ...

- ☐ Baseline BP subgroups
- ☐ BP Outlier status
- ☐ Hypertension AEs
- ☐ BP as a covariate
- ☐ BP at visit 1 or at visits 1 and 2

Analysis of Confirmed Thrombotic CV Events by Change in MAP at Week 4

Change from baseline BP	Placebo (N=1297) Events/Patient-years (ratex100), N	Rofecoxib (N=1287) Events/Patient-years (ratex100), N	Relative Risk (95% CI)
Overall	25/3302 (0.757), 1281	45/3038 (1.481), 1266	1.952 (1.197, 3.183)
<-4.6	6/1031 (0.582), 400	8/615 (1.300), 256	2.226 (0.772, 6.416)
-4.6 to 0	7/878 (0.798), 343	13/802 (1.621), 334	2.020 (0.806, 5.063)
0 to 5.8	7/711 (0.985), 275	7/760 (0.921), 321	0.931 (0.326, 2.654)
>5.8	5/676 (0.739), 261	17/861 (1.975), 355	2.669 (0.985, 7.234)

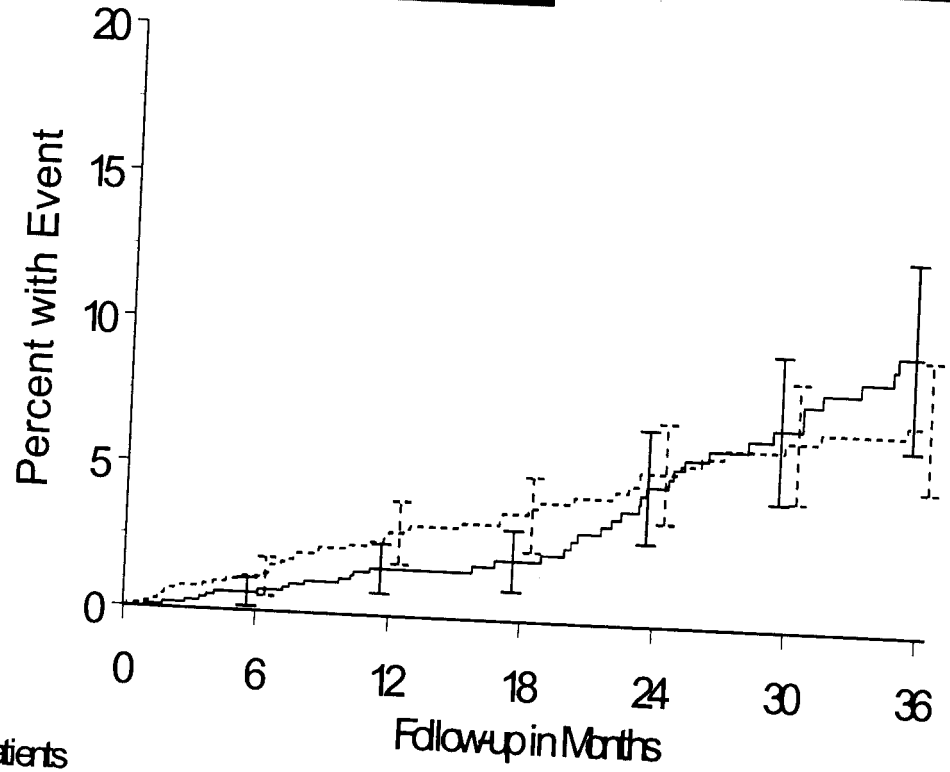
CV Results from Alzheimer's Protocols 078 + 091 Combined

Submitted to IND 46,894 on DATE
Submitted to NDA 21-042 on DATE

Confirmed Serious CV Adverse Events in PN078

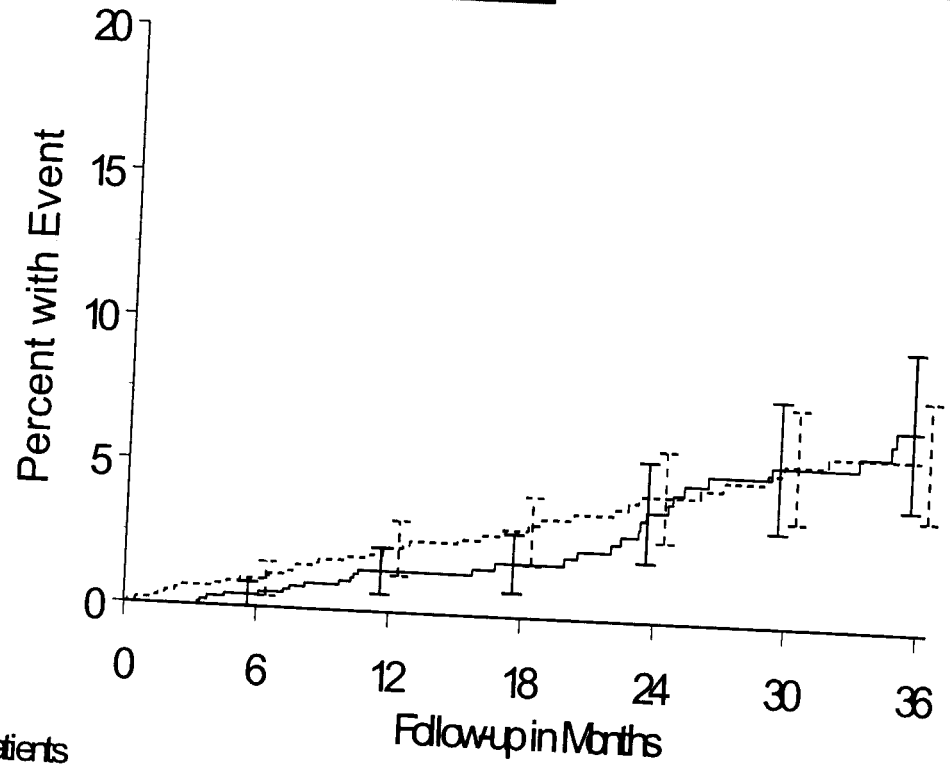
- Thrombotic vascular events
  - 38 for rofecoxib, 36 for placebo
  - ischemic stroke: 6 for rofecoxib, 13 for placebo
  - transient ischemic attack: 7 for rofecoxib, 3 for placebo
  - myocardial infarction: 13 for rofecoxib,10 for placebo
- Hemorrhagic strokes
  - 1 for rofecoxib, 2 for placebo

Data from AD Protocols 078 + 091 Combined – Confirmed Thrombotic



Number of Patients							
Placebo	1074	939	797	463	385	283	243
Rofecoxib 25 mg	1069	878	707	415	318	226	185

Data from AD Protocols 078 + 091 Combined – APTC Endpoint



Number of Patients							
Placebo	1074	941	802	466	389	287	247
Rofecoxib 25 mg	1069	880	708	416	320	228	188

APPROVe: Summary

- A difference from placebo in CV events was not observed through 18 months of treatment.
- After 18 months, a significant increase was noted for more CV events which increased over time in the patients administered VIOXX relative to those administered placebo.
- The mechanism for this increased risk is uncertain.
- As a result of this new safety information, Merck is voluntarily withdrawing VIOXX worldwide and initiating a product pullback in the US to the pharmacy level.