Fendelander, Helene C

From: Bain, Raymond P.
Sent: Wednesday, October 31, 2001 12:37 PM
To: Reines, Scott A.; Nies, Alan S.; Gertz, Barry J.; Williams, George W(U.S.)
Subject: RE: CV Analysis for Alzheimer's Protocol

In preparation for the meeting outlined below on analysis for the Alzheimer's Disease protocols, the attached document summarizes the current status of the three AD protocols including a summary of the competed mortality analyses.

Ray

Mortality_Summary.doc

Raymond P. Bain, PhD
Vice President
CBARDS-BL
Phone (484)344-7589
Fax (484)344-4028
E-mail: raymond_bain@merck.com

-----Original Message-----
From: Inoa-Gonzalez, Carmen
Sent: Wednesday, October 31, 2001 11:26 AM
To: Inoa-Gonzalez, Carmen; Bielesch, Nancy A.; Fendelander, Helene C; Banion, Linda J; Gilchrist, Cynthia L
Cc: Reines, Scott A.; Bain, Raymond P.; Nies, Alan S.; Gertz, Barry J.; Williams, George W(U.S.)
Subject: CV Analysis for Alzheimer's Protocol

This is to confirm the following meeting:

RE: CV Analysis for Alzheimer's Protocol
Date: Tuesday, November 6, 2001
Time: 4:30 - 5:00 p.m.
Location: Alan Nies's office (Gertz, Nies)
Scott Reines's office (Reines, Bain, Williams)

[Helene will place the call to Scott's office - 344-2608]

Carmen Inoa-Gonzalez

Administrative Associate
to Dr. Barry J. Gertz, Vice President
Phone: 732-594-5411
Fax: 732-594-7310
carmen_inoa@merck.com

EXHIBIT
tabbies
362

SUMMARY OF MORTALITY ANALYSES
VIOXX ALZHEIMER'S DISEASE

First Treatment Trial (Protocol -091)
Second Treatment Trial (Protocol -126)
Prevention Trial (Protocol -078)

Prepared by
Raymond P. Bain, PhD.
Vice President, CBARDS-BL

October 31, 2001

First Treatment Trial (Protocol -091):

Status:

- Completed.
- Frozen File 2/2001
- Full CSR: Stat results to Clinical 11/15/2001

Protocol:

- Evaluate the efficacy and safety of MK-0966 25 mg on slowing progression of AD
- At least 50 years of age with possible or probable AD
- MK-0966 25 mg or placebo for 12 months
  Three-month randomized withdrawal (90% of MK-0966 assigned placebo)
- Patients who discontinue study drug are required to return for routine study visits for the duration of the trial
- Safety Section: "All patients who take study medication will be included in the analysis of safety...compare the incidence of clinical adverse events occurring in the initial 12-month treatment period".

Approved DAP:

- All patients who are randomized will be included in the safety analysis
- "The primary safety endpoint is the incidence of clinical adverse experiences reported by the patients from randomization up to 12 months. The clinical AEs over the entire study will be summarized separately." [Note: AE counts tables will be provided for the three-month randomized withdrawal separately]
- "For each study time period, 2 approaches will be used for AE summary. First, a primary analysis will include all AEs when patients are on treatment and up to 14 days following discontinuation of test therapy. Second, a summary based on intention-to-treat approach will include all AEs regardless of on or off study therapy".
- Seven pre-specified clinical adverse experiences (Tier I AEs)

Second Treatment Trial (Protocol -126):

Status:

- Discontinued based on the results of protocol -091
- Frozen File 8/2001
- Abbreviated CSR: Stat safety results to Clinical 11/15/2001

Protocol:

- See -091

DAP:

- No DAP given abbreviated CSR

Prevention Trial (Protocol -078):

Status:

- Ongoing
- LPI 3/31/1999
- LPO expected end 2002 (event driven)

Protocol:

- Evaluate the efficacy and safety of MK-0966 25 mg on the prevention of AD
- At least 65 years of age with mild cognitive impairment
- MK-0966 25 mg or placebo for 4 years or until 220 cases of clinically-diagnosed probable or possible AD
- Patients who discontinue study drug are required to return for routine study visits for the duration of the trial
- Safety Section: "All patients who take study medication will be included in the analysis of safety"

DAP:

- DAP was approved by BARDS, Clinical Research, Worldwide Editing and Regulatory Affairs in May to June 2000. The DAP was not forwarded to word processing pending discussions with the FDA regarding the primary efficacy analysis (ie., LOCF verses longitudinal data analysis).
- "Two approaches will be used for AE summary. First, a primary analysis will include all AEs when patients are on treatment and up to 14 days following discontinuation of test therapy. Second, a summary based on intention-to-treat approach will include all AEs regardless of on or off study therapy".

- Issue: ISS DAP.

Definition of Mortality Events:

- On Drug: Event on study medication and up to 14 days after the last dose of medication.
- On Study: Event during follow-up (on or off study medication) and up to 14 days following discontinuation of study visits (aka ITT).
- On Drug - SUR: Event on study medication and up to 14 days after the last dose of medication including patients who developed SAEs within 14 days of the last dose of study medication and then died more than 14 days after the last dose of study medication [Note: SAE must be continuing past last dose of study medication and SAE must be "linked" to the mortality event based on clinical judgment.]

Baseline Characteristics:

	MK-0966	Placebo
Protocol -091:		
Randomized	346	346
Female gender (%)	54.1	52.3
Mean Age, in years (SD)	75.6 (8.3)	75.0 (8.8)
Protocol -126:		
Randomized	382	376
Female gender (%)	50.8	49.5
Mean Age, in years (SD)	75.4 (8.3)	75.2 (7.9)
Protocol -078:		
Randomized	723	732
Female gender (%)	34.2	31.2
Mean Age, in years (SD)	75.1 (6.0)	74.8 (6.0)

Mortality Analyses: History of Reports

Date of Memo	Protocols*	Type of Analysis	Mortality Outcome	Follow-up
4/4/01	091	On Study ***On Drug***	All-Cause	***0-12 Months*** 0-15 Months
4/8/01	078	On Study On Drug	All-Cause	All as of 3/23/01
4/8/01	078+091	On Study On Drug	All-Cause	091: 0-12 Months 078: All as of 3/23/01
5/1/01	078+091+126	On Study On Drug	All-Cause	091: 0-12 Months 078: All as of 3/23/01 126: All as of 4/19/01
10/4/01	078 091 126	On Drug-SUR	All-Cause CV	091: Pla/Pla: 0-15 Months 091: MK/MK: 0-15 Months 091: MK/Pla: 0-12 Months 078: All as of 3/16/2001 126: All as of 3/16/2001
10/19/01	078+091+126	On Drug-SUR	All-Cause CV	091: Pla/Pla: 0-15 Months 091: MK/MK: 0-15 Months 091: MK/Pla: 0-12 Months 078: All as of 3/16/2001 126: All as of 3/16/2001

* -091 1st treatment trial; -126 2nd treatment trial; -078 Prevention trial

Mortality Analyses: Results

Protocol	Type	Outcome	MK-0966*	Placebo*	p-value (log-rank)	Crude Ratio**
091	On Study	All-Cause:0-12	13/346 (0.042)	3/346 (0.009)	0.010	4.67
	On Study	All-Cause:0-15	15/346 (0.039)	8/346 (0.020)	0.142	1.95
	On Drug	**All-Cause:0-12**	**9/346 (0.030)**	**2/346 (0.006)**	**0.028**	**5.00**
	On Drug	All-Cause:0-15	9/346 (0.030)	4/346 (0.011)	0.049	2.72
	On Drug-SUR	All-Cause	14/346 (0.046)	8/346 (0.022)	0.056	2.09
	On Drug-SUR	CV	3/346 (0.010)	3/346 (0.008)	0.xx	1.25
078	On Study	All-Cause	21/723 (0.018)	9/732 (0.007)	0.015	2.57
	On Drug	**All-Cause**	**13/721 (0.013)**	**7/729 (0.006)**	**0.10**	**2.17**
	On Drug-SUR	All-Cause	15/721 (0.015)	9/729 (0.008)	0.12	1.87
	On Drug-SUR	CV	5/721 (0.005)	2/729 (0.002)	0.19	2.50
126	On Study	All-Cause	4/382 (- - -)	4/376 (- - -)	- - -	- - -
	On Drug	**All-Cause**	**3/381 (- - -)**	**3/376 (- - -)**	- - -	- - -
	On Drug-SUR	All-Cause	4/381 (0.024)	3/376 (0.018)	0.66	1.33
	On Drug-SUR	CV	2/381 (0.012)	1/376 (0.006)	0.55	2.00
078+091	On Study	All-Cause	34/1069 (0.023)	12/1078 (0.008)	<0.001	2.87
	On Drug	All-Cause	22/1067 (0.017)	9/1075 (0.006)	0.008	2.83
078+091+126	On Study	All-Cause	38/1451 (0.023)	16/1454 (0.009)	0.001	2.56
	On Drug	**All-Cause**	**25/1448 (0.017)**	**12/1451 (0.007)**	**0.015**	**2.43**
	On Drug-SUR	All-Cause	33/1448 (0.022)	20/1451 (0.012)	0.026	1.83
	On Drug-SUR	CV	10/1448 (0.007)	6/1451 (0.004)	0.21	1.75

* Number of events/number included in the analysis with the event rate per patient-year of follow-up in parentheses

** Ratio (MK-0966/Placebo) of mortality event rates (per patient-year of follow-up)