

To: Shapiro, Deborah R.; Bolognese, James A.; Sperling, Rhoda; Reicin, Alise S.; Oppenheimer, Leonard; Barr, Eliav; Gertz, Barry J.; Nies, Alan S.  
From: Morrison, Briggs W  
Cc: Curtis, Sean P.  
Bcc:  
Date: 2001-08-17 17:58:23  
Subject: RE: FOR REVIEW [PEER]: 2001-ms-2470 (FULL PAPER) - DUE DATE MONDAY, 27 AUGUST 2001

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As I said, they are discretionary comments. I do understand why the paper is written as it is and I am not an author. I submit these comments only as a surrogate for a minimally informed reviewer.

I understand Jim's "if only..." argument, but one could also "if only" add events to rofe and solidify an alternative interpretation. I guess my point is that one usually discusses the limitations of the paper - one of the limitations here is the paucity of data and therefore "conclusions" may be too strong a word; "there in no evidence" also seems (to me) to be a bit of a stretch. This is at best hypothesis-generating level information. And if we are hypotheses generating, a slightly different look at the data could suggest alternative hypothesis - the placebo data is driven by Alzheimers and the RR for alzheimers is qualitatively different than for the other diseases - is there a biological difference between the alzheimer's population and OA, RA, LBB?. These issues are not discussed. Finally, I understand that a "decision was made" to pool in certain ways, but doesnt one have an obligation to re-examine the rationale behind that decision as data accrues. That is what I meant about "fitting the data to a hypothesis" rather than letting the data generate hypotheses.

bwm

-----Original Message-----

From: Shapiro, Deborah R.  
Sent: Friday, August 17, 2001 11:42 AM  
To: Bolognese, James A.; Morrison, Briggs W; Sperling, Rhoda; Reicin, Alise S.; Oppenheimer, Leonard; Barr, Eliav; Gertz, Barry J.; Nies, Alan S.  
Cc: Curtis, Sean P.  
Subject: RE: FOR REVIEW [PEER]: 2001-ms-2470 (FULL PAPER) - DUE DATE MONDAY, 27 AUGUST 2001

I agree with Jim's points and perhaps they could be added to the discussion or presentation of results because I believe other readers as well will have the same concerns as Briggs expressed. The statistical models (both Cox for indications and Zelen's test for protocols) said these could be pooled because these outliers were so small. The easiest way to explain that to a non-statistical audience is with examples such as Jim provided. By the way, the decision was made early on to split the indications into OA, RA and Others-- the others we had at the time were ALZ and LBP, recently the update also included prostatitis.

Deborah  
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-----Original Message-----

From: Bolognese, James A.  
Sent: Friday, August 17, 2001 11:35 AM  
To: Morrison, Briggs W; Sperling, Rhoda; Reicin, Alise S.; Shapiro, Deborah R.; Oppenheimer, Leonard; Barr, Eliav; Gertz, Barry J.; Nies, Alan S.  
Cc: Curtis, Sean P.  
Subject: RE: FOR REVIEW [PEER]: 2001-ms-2470 (FULL PAPER) - DUE DATE MONDAY, 27 AUGUST 2001

Good points, Briggs - of course your suggestions are plausible, but based on too-small numbers, I think. Here's another perspective . . .

If only 1 more event were observed in RA on placebo and 1 more event observed in OA on placebo, then the RR's would be 0.89 in RA 1.06 in OA - in line w/ the ALZ and non-naproxen NSAID results. Thus, my opinion is that the RR's for OA and RA are unreliable & based on too-small numbers to be used to suggest trends. It also points out how the overall RR for rofe vs. placebo is driven largely by ALZ.

So, I think the critical review of the data is largely based on the bulk of the data which divide into two independent large chunks - rofe vs. placebo in ALZ, and rofe vs. non-naproxen in OA, both of which consistently suggest no negative impact of rofe. So, I think the conclusion is appropriate.

Jim

-----Original Message-----

From: Morrison, Briggs W

Sent: Friday, August 17, 2001 11:13 AM

To: Rhoda Sperling (E-mail); Alise Reicin (E-mail); Shapiro, Deborah R.; Oppenheimer, Leonard; Barr, Eliav; Gertz, Barry J.; Nies, Alan S.; Bolognese, James A.

Cc: Curtis, Sean P.

Subject: FW: FOR REVIEW [PEER]: 2001-ms-2470 (FULL PAPER) - DUE DATE MONDAY, 27 AUGUST 2001

I have signed off on the attached manuscript for clearance. However I would like to raise an issue.

If we look at Table 3 and look at rofe vs placebo relative risks

RA	1.78
OA	1.53
ALZ/CLBP	0.68

Now look at relative risk of rofe vs Naproxen

RA	1.74
OA	1.5

And rofe vs non-nap NSAIDs

OA	0.79
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A few things

1. The rofe vs placebo in OA and RA - albeit with small numbers - looks alot like the etori figures vs placebo. Is alz the outlier?
2. Why is CLBP with Alzeihmers? I understand CLBP is small numbers, but I dont think the demographics justify pooling those 2.
3. We say there is no "significant heterogeneity across indications" in the placebo group, but the RR's are qualitatively different in RA/OA va Alz. I guess statistics says you can pool those, but there isnt even a mention that perhaps there are biologic differences between patient populations and that in fact these should not be pooled.
4. It is striking how consistent the RR is in RA for rofe vs placebo and rofe vs nap; same is true in OA (is OA non-nap NSAIDs the outlier?). It seems to me an equally reasonable interpretation is that it is rofe vs any comparator.

I guess what I am saying is that the data appears to have been interpreted to support a preconceived hypothesis rather than critically reviewing the data to generate hypotheses. The Second line of the Discussion says "There was no evidence (emphasis mine) that rofecoxib was associated with excess CV events compared with either placebo or non-naproxen NSAIDs" - that seems wishful thinking, not a critical interpretation of the data. Of course if you look at Figure 1, the 95% CIs for all comparisons include the possibility that there is a real

increases risk on rofecoxib.

These comments are discretionary.

bwm

-----Original Message-----

From: OSTIC Correspondence

Sent: Wednesday, August 15, 2001 8:12 AM

To: Altmeyer, Anne; Erb, Dennis M.; Lewis, Suzanne Gregory; Margolskee, Dorothy J; Oppenheimer, Leonard; Panzer, Curtis C.; Williams, George W(U.S.); Morrison, Briggs W

Cc: Harper, Sean E.; Beauchard, Lucine E.; Bourdow, Carrie L.; Cohn, Judith; DeTora, Lisa M; El-Dada, Riad H.; Griffing, William J.; Kasperzik, Jens; Melin, Jeffrey M; Skidmore, Janet G; Yates, John; DiBattiste, Peter M.; Murphy, Gail; Truitt, Ken E; Cole, Gwyn; Ford-Hutchinson, Anthony; Simon, Thomas J.

Subject: FOR REVIEW [PEER]: 2001-ms-2470 (FULL PAPER) - DUE DATE MONDAY, 27 AUGUST 2001

FOR REVIEW: ALTMAYER, ANNE; ERB, DENNIS M.; LEWIS, SUZANNE GREGORY; MARGOLSKEE, DOROTHY J; MORRISON, BRIGGS W.; OPPENHEIMER, LEONARD; PANZER, CURTIS C.; WILLIAMS, GEORGE W

FYI: MURPHY, M. GAIL; TRUITT, KENNETH E; HARPER, SEAN E.; BEAUCHARD, LUCINE; BOURDOW, CARRIE L.; COHN, JUDITH; COLE, W. GWYN; DETORA, LISA; EL-DADA, RIAD H.; FORD-HUTCHINSON, ANTHONY W.; GRIFFING, WILLIAM J.; KASPERZIK, JENS; MELIN, JEFFREY; SIMON, THOMAS JAY; SKIDMORE, JANET; YATES, JOHN; DIBATTISTE, PETER M.

PLEASE REVIEW THE ATTACHED MANUSCRIPT AND RETURN IT WITH YOUR COMMENTS BY MONDAY, 27 AUGUST 2001.

2001-ms-2470

KONSTAM, M.A., WEIR, M.R., SHAPIRO, D.R., REICIN, A.S., SPERLING, R.S., BARR, E. and GERTZ, B.J.

Cardiovascular thrombotic events associated with rofecoxib: A pooled analysis of patient level data.  
data. For submission to: JAMA Express.

<< File: WMA71218.DOC >>

Please contact CAROLINE THOMPSON at 732-594-7871 (fax 732-594-3868) for questions regarding this manuscript.

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