Reviewer's report

Title: Celecoxib Concentration Predicts Decrease In Prostaglandin E2 Concentrations In Nipple Aspirate Fluid From High Risk Women

Version: 1 Date: 18 June 2007

Reviewer: Peter Gann

Reviewer's report:

General

This paper represents a re-analysis of data from the same trial, which was reported in two earlier publications (one with the 200 mg celecoxib dose and the other with the 400 mg group). Overall, this analysis, which looks at the change in NAF and plasma PGE2 concentrations in relation to the post-treatment celecoxib level in plasma, adds very little to the previous publications. In addition, the manner in which the data and statistical analyses are presented does not provide an adequate basis for interpretation by readers, especially given the very large range in celecoxib concentrations reported. There is some question as to whether the statistical power is sufficient for some of the conclusions drawn.

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

1. As noted above, simply evaluating the relationship of PGE2 change to celecoxib level does not seem to constitute a very large knowledge increment. These results could have been included in the 2006 paper.

2. p. 6. More detail regarding the processing of the NAF samples seems indicated. How were samples cleaned up? Was extraction performed? In addition there should be some information regarding assay quality control procedures (CVs, duplicate measures, QC samples, etc.)

3. p. 9. Absence of any data on pre-treatment celecoxib levels is surprising. These might have been eliminated due to cost, but these data would have assured the reader re: specificity of the assay and lack of contamination by off-study drug use.

4. p. 9. The range in plasma drug levels in the 400 mg group was over 100-fold. This will create problems in the data analysis (see below) and begs the question as to the explanations for such extreme variability.

5. p. 9. The use of non-parametric statistics seems appropriate for generating P values given what must be an extremely non-normal data distribution for celecoxib and perhaps PGE2 as well. The paper provides no information regarding the actual magnitude of change within-person (in fact this may be problematic if variability is extreme). Figure 1, which provides rankings only, does not allow the reader to see what these relationships really look like. The authors state that NAF PGE2 and plasma celecoxib were related similarly in pre- and post-menopausal women – but Table 2 shows that the median PGE2 level actually increased after treatment in pre-menopausal women at both dose levels. This anomaly could be explained by an extremely odd distribution of the data, with high variance.

6. Table 2. It is not clear what delta-PGE2 column heading means – is this a mean or median delta? As a result, it is also not clear what the P value for delta PGE2 means.

7. p. 9. The text states that there was no significant difference in PGE2 response in pre- and post-menopausal women. The basis for this statement is not given, and the power for making this comparison must be extremely low.


9. p. 11. The median celecoxib level in pre-menopausal women on 200 mg dose changed from 195 to 117 (Table 2 vs Table 3) with the subtraction of just one subject. This indicates that the point estimates for
concentrations are very unstable, especially when based on medians involving only 5-6 subjects.

10. p. 12. The conclusion that there exists a threshold for celecoxib action between given plasma levels does not seem supportable, in view of the study size and data anomalies described above.

11. p. 12. It is not clear how the authors have excluded the possibility that PGE2 levels in NAF (or plasma) reflect COX-1 activity, perhaps to a greater degree than does COX-2 activity.

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

1. p. 4. Paper should give either ng/ml or ?M, or both, but should not switch.

2. The statement regarding reference 7 gives the impression that long-term celecoxib use was shown to reduce breast cancer risk in a human trial; in fact, this was an observational study and the statement should reflect that.

Discretionary Revisions (which the author can choose to ignore)

What next?: Reject because too small an advance to publish

Level of interest: An article of limited interest

Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests: I declare that I have no competing interests.