Daniel B Burnham on 18-Nov-1999 11:33

Clinical R&D North America Upper Providence Redacted

To: rajinder kumar, charles altman
cc: thomas kline, katherine lenard-dittman, Eva Nystrom, david seymour, barry brand
Subject: Incidence of death/suicide in paroxetine randomized controlled trials in depression: FDA request

Raj and Chip, attached is a draft of the cover letter FDA_deaths.DOC and Excel spreadsheet

FDA_deaths.xls that now includes the additional deaths that occurred during the placebo run-in phase of randomized controlled paroxetine depression trials.

The 2 suicides among the 544 placebo patients in Montgomery and Dunbar's 1995 publication actually occurred during single-blind placebo run-in, not double-blind placebo.

Because patients undergo usually 1 week of single-blind run-in *before* randomization, these 2 suicides on placebo are not comparable to deaths occurring after randomization for 3 reasons.

- First, the pre- and post-randomization populations are different because patients who respond to single-blind placebo are excluded from randomization.
- Second, an incidence of placebo run-in deaths is difficult to determine because the number of patients who underwent placebo run-in is not simply the total number of patients randomized.
- Third, even if the number in run-in were known, the incidence of deaths would not be able to be compared to the incidence on randomized medication because the duration of exposure on the latter on average is much greater than on 1-week's worth of run-in placebo.

**Bottom line: we must mention the placebo run-in deaths to reconcile the overall incidence figures with the Montgomery and Dunbar publication. However, we cannot combine these placebo *run-in* deaths with the *randomized* placebo death rate for the 3 reasons above. Thus, we are left with a 0.1% suicide rate on paroxetine IR and a 0% rate on placebo.**

One death in an old Novo Nordisk study (097) still needs to be unblinded as to double-blind treatment, despite our Scandinavian office trying to get the records from Novo Nordisk for 2 months. Because study 097 was locally funded, this case will not affect the death and suicide rates determined for centrally funded studies.

Regards-Dan