23. QUESTION 23

Provide an explanation for the high incidence of adverse events of emotional lability from Group 1 in the repeated dose healthy volunteer studies.

Response

In the original response, it is stated "In Group 1, there were 3 reports from a total of 395 volunteers of "Emotional lability" following single doses of paroxetine and 24 reports from a total of 110 volunteers following repeated dosing with paroxetine. There were also 7 reports of "Emotional lability" from a total of 65 volunteers following repeat dosing with placebo".

The GSK centrally-databased studies in healthy volunteers have been searched for adverse events relating to "suicide" and self-harm". Although, some events of emotional lability were found, none of them satisfied the predetermined search criteria for "possibly suicide-related events" or "self harm".

In these studies, a standard symptom checklist was used, and the verbatim term for these events was "mood change" in all cases. The data in question are contained in Table 3 from Appendix 2A of the original response. In this set of studies, adverse event data were collected largely by symptom checklist which was completed by the subject, although spontaneous reports by subjects or supervising medical staff could also be reported in the case report form. The symptom checklists were presented to the subjects at times specified in the protocol, so several may have been completed in a single day by a volunteer. The subject was instructed to indicate whether or not a symptom was present, and, if so, to record further details of that symptom on the back of the form (e.g. severity, duration).

The preferred term "Emotional Lability" is assigned from the ADECS code JDNQC, ADECS being the adverse event coding system in use by SmithKline Beecham at the time of the original depression MAA/NDA submission. Examination of the verbatim terms recorded against the ADECS code "JDNQC" reveals that all events reported were described as either "mood change" (which is one of the symptoms listed on the symptom checklist) or "change in mood".

The following table summarises the data on "Emotional Lability":

Table 23.1 Group 1 – Percentage of Volunteers Reporting Emotional Lability Adverse Events from Repeat Dose Studies (Excerpt from Table 3 from Appendix 2A).

	Predose	Week 1	Week 2	Week 3	Week 4	Week 4+	Follow-up
Placebo	0	6	10	5	0	0	0
Paroxetine	1	10	3	2	3	0	8

The figures in the table were derived by dividing the number of events reported by the number of volunteers dosed for each time period, so are not a true measure of incidence in cases where a volunteer reported the event more than once in a time period. The figure given for week 1 following paroxetine administration (10%) is actually an overestimate in terms of percentage of volunteers reporting "emotional lability", since two volunteers receiving paroxetine reported the event more than once in the first week, so the actual percentage of volunteers reporting the adverse event in week 1 following paroxetine administration is only 8%, compared with 6% for those who received placebo treatment. All other percentage figures for "emotional lability" are unaffected in Table 3 of Appendix 2A, since in those cases events were reported only once by each volunteer. In weeks 2 and 3, the incidence following placebo treatment is higher than that following paroxetine treatment, but generally the reporting rates were low. One volunteer reported "mood change" prior to dosing with paroxetine, but not after paroxetine administration. The figures for "emotional lability" should therefore read as follows, with the actual numbers of volunteers reporting the event for clarity:

Table 23.2 Group 1 – Amended Percentage (numbers) of Volunteers Reporting Emotional Lability Adverse Events from Repeat Dose Studies

	Predose	Week 1	Week 2	Week 3	Week 4	Week 4+	Follow-up
Placebo	0% (0/65)	6% (4/65)	10% (2/21)	5% (1/20)	0% (0/8)	0% (0/2)	0% (0/53)
Paroxetine	1% (1/110)	8% (9/110)	3% (3/91)	2% (1/62)	3% (1/31)	0% (0/16)	7% (8/107)

Overall, the percentage of volunteers reporting emotional lability adverse events is similar within each treatment group during weeks 1-4 on treatment. Of the 8 volunteers reporting "emotional lability" in the follow-up phase after paroxetine administration, 5 had previously reported the event during the active dosing phase of the study, so only 3 volunteers reported it after discontinuation of paroxetine.

Taking into account the repeat event reports by individual volunteers and the single event reported prior to paroxetine administration, the actual overall incidence of "emotional lability" in this dataset (defined as the number of individual volunteers reporting the event divided by the number of volunteers dosed) is 15.4% (17/110 volunteers) after paroxetine administration and 10.8% (7/65) after placebo administration.

Overall, our conclusion has not changed for this dataset.The GSK centrally-databased studies in healthy volunteers have been searched for adverse events relating to "suicide", and "self-harm". Although, some events of "emotional lability" were found, none of them satisfied the predetermined search criteria for "possibly" suicide-related events or "self-

harm". There is no evidence from the healthy volunteer studies within this review to link paroxetine with possibly suicide related events or self harm.