QUESTION 5

From the answers provided to the previous CPMP Lists of Questions it was noted that some studies had been excluded from the analyses. The MAHs should provide a summary of the safety data from these studies, particularly the data relating to suicide, suicidal thoughts and self-harm, unless the MAHs confirm that these data were included in the MAHs' safety database and have already been provided as such during this referral procedure.

Response

1.1. Introduction

The response to Question 3 submitted in early February 2004 described controlled studies with paroxetine that are not included on the GSK central R&D aggregated database. As was described in that previous response, in many cases these studies have been conducted or sponsored by SmithKline Beecham/GlaxoSmithKline local affiliate companies, including local Phase IIIB and Phase IV clinical trials, but they also include a centrally sponsored full development programme of paroxetine for the treatment of depression, panic disorder, obsessive compulsive disorder, and social anxiety disorder conducted in Japan. In general, the data collection methods employed in these studies do not allow information from these studies to be readily merged into the central R&D aggregated database. In some cases the study design does not allow the study information to be merged with the paroxetine database datasets (e.g. studies with intermittent therapy for the treatment of premenstrual dysphoric disorder (PMDD)).

In total, we quoted 22 company-sponsored controlled studies (now amended, see Section 1.2.1) involving approximately 3700 patients, that have been reported but not included in the central R&D database. The Japanese development programme accounted for almost half of these figures, with, we believed, 10 controlled studies in Japan involving almost 1700 Japanese patients. The studies are in a variety of indications including depression, OCD , panic disorder and PMDD and include investigations into potential advantages of co-administering paroxetine with pindolol.

Although these studies are not on the central R&D aggregated database, any serious adverse experiences from these studies will have been reported centrally and included in the paroxetine Periodic Safety Update Reports as appropriate; thus any serious adverse events from these additional studies which were deemed by the investigator to have a causal association with study medication will have been available to Regulatory Authorities worldwide.

It has not been possible in the time available to provide an extensive summary of the safety data from these studies. An initial overview of safety data from these studies is provided below (Section 1.2.2), but it is restricted and focussed only on data relating to suicide, suicidal thoughts or self-harm. Study reports or synopses are available electronically for many of these studies (and are provided within the electronic CD-ROM version of this response – 15 out of 21 studies) and can be provided immediately on

request. Others are paper only, would have to be copied or scanned, but could be provided if requested.

1.2. Description of the studies

The 22 "controlled" studies mentioned above, are listed below:

Study 056 (UK)

A double-blind, multicentre parallel group study in General Practice comparing the efficacy and tolerability of paroxetine with that of dothiepin in the treatment of elderly depressed patients

Patients randomised: 134 (67 to paroxetine, 67 to dothiepin)

Study 092 (UK)

A double-blind, between patient, multicentre study comparing the efficacy, tolerability and effects on cognitive function of paroxetine with those of lofepramine in depressed patients in General Practice

Patients randomised: 138 (70 to paroxetine, 68 to lofepramine)

Study 097 (Denmark)

ECT and paroxetine / imipramine combination treatment in depressive states. A clinical study of the safety of co-administration of ECT and paroxetine or imipramine, and relapse prevention in the maintenance phase.

Patients randomised: 87 (45 to paroxetine, 25 to imipramine, 17 to placebo)

Study 323 (Japan)

Early phase II open study of the efficacy and safety of paroxetine hydrochloride in patients with depression or depressive episodes

Number of patients: 62 (all paroxetine)

Study 324 (Japan)

Open, multicentre study to assess the efficacy and safety of paroxetine in patients with OCD

Number of patients: 38 (all paroxetine)

Study 325 (Japan)

A double-blind, multicentre group comparison, dose finding study to determine the optimal dose range of paroxetine, versus imipramine, for the treatment of patients with depression or depressive episodes

Patients randomised: 138 (41 to paroxetine low dose, 45 to paroxetine high dose, 52 to imipramine)

Study 332 (Belgium, Germany, Ireland, Italy, UK)

A double-blind, multicentre study to assess the efficacy and tolerability of paroxetine and amitriptyline in patients with a mild, moderate or severe depressive episode associated with rheumatoid arthritis

Patients randomised: 191 (94 to paroxetine, 97 to amitriptyline)

Study 338 (Japan)

A double-blind multicentre study to assess the efficacy and safety of paroxetine compared with amitriptyline in patients with depression or depressive episodes

Patients randomised: 228 (109 to paroxetine, 119 to amitriptyline)

Study 384 (Japan)

A double-blind, multicentre, placebo controlled, parallel group study of the efficacy, safety and usefulness of paroxetine in patients with panic disorder

Patients randomised: 171 (87 to paroxetine, 84 to placebo)

Study 391 (Netherlands)

A double-blind study of the effects of paroxetine, fluoxetine and placebo on driving ability in healthy volunteers

Subjects randomised: 24 (balanced order; each subject to receive all treatments)

Study 402 (Italy, Belgium, Germany, Austria, Canada)

A double-blind, multicentre, parallel group study of paroxetine and amitriptyline in the treatment of patients with depression associated with breast cancer

Patients randomised: 179 (89 to paroxetine, 90 to amitriptyline)

Study 410 (Japan)

A double-blind, multicentre, placebo controlled, parallel group study to determine the optimal dose range for paroxetine for the treatment of panic disorder

Patients randomised: 132 (42 to paroxetine low dose, 49 to paroxetine high dose, 41 to placebo)

Study 414 (Japan)

A placebo controlled, double-blind, multicentre and dose-finding study to provide an optimal dose of paroxetine in patients with OCD

Patients randomised: 119 (60 received paroxetine, 56 received placebo)

Study 447 (Japan)

A double-blind, parallel group comparison of the efficacy, safety and usefulness of paroxetine and trazodone in patients with depression or depressive episodes in the fields of internal medicine and psychosomatic medicine

Patients randomised: 238 (122 to paroxetine, 116 to trazodone)

Study 511 (France)

Multicentre, randomised, double-blind study comparing the efficacy and tolerability of DEROXAT (paroxetine) and ANAFRANIL (clomipramine) in the treatment of major unipolar depression in adolescents aged 12 to 20 years

Patients randomised: 121 (63 to paroxetine, 58 to clomipramine)

Study 512 (UK)

A multicentre, double-blind, placebo controlled study to investigate the effect of pindolol on the onset of antidepressant activity of paroxetine in the treatment of depression

Patients randomised: 167 (83 to paroxetine + pindolol, 84 to paroxetine + placebo)

Study 518 (UK)

A multicentre, double-blind, double dummy, randomised controlled study to investigate the speed of onset, safety, efficacy and tolerability od paroxetine in combination with pindolol compared with dothiepin in the treatment of depression

Patients randomised: 211 (105 to paroxetine + pindolol, 106 to dothiepin)

Study 526 (China)

Double-blind, multicentre randomised drug-controlled verification study comparing the efficacy and safety of paroxetine versus clomipramine in treating patients with Obsessive Compulsive Disorder and Panic Disorder

Patients randomised: 209 (109 to paroxetine, 100 to clomipramine)

Study 658 (Sweden)

A placebo controlled study to investigate the efficacy of intermittent and continuous treatment with paroxetine in patients with Premenstrual Dysphoric Disorder (PMDD)

Patients randomised: 186 (61 to paroxetine intermittent treatment, 63 to paroxetine continuous treatment, and 62 to placebo)

Study 660 (Japan)

A double-blind, placebo-controlled, multicentre study of paroxetine in the treatment of Obsessive Compulsive Disorder

Patients randomised: 191 (95 received paroxetine, 94 received placebo)

Study 661 (Japan)

A double-blind, placebo controlled, multicentre study of paroxetine in the treatment of Social Anxiety Disorder

Patients randomised: 353 (117 to paroxetine 20mg, 116 to paroxetine 40mg, 120 to placebo)

Study 717 (Canada, Finland, Germany, Netherlands, Norway, Sweden, USA)

A double-blind, placebo controlled, 3-arm fixed dose study of paroxetine CR intermittent dosing (12.5mg and 25mg) for Premenstrual Dysphoric Disorder

Patients randomised: 373 (131 to paroxetine CR 12.5mg, 119 to paroxetine CR 25mg, 123 to placebo)

1.2.1. Summary of additional exposure to paroxetine

In total, 3690 subjects were enrolled in these 22 studies, and 2190 of the subjects were allocated treatment with paroxetine. Two of the Japanese studies (studies 323 and 324) were in fact open, uncontrolled trials, and study 391 was a controlled study in healthy volunteers. Omitting those studies, there were 2066 patients allocated to paroxetine treatment in controlled studies that were not part of the central R&D aggregated database.

1.2.2. Data relating to suicide, suicidal thoughts and self-harm

Data from the above 22 studies have been examined with particular focus on data relating to suicide, suicidal thoughts and self-harm.

1.2.2.1. Adult studies

Twenty-one of the 22 studies were conducted in adults. Adverse events possibly relating to suicide, suicidal thoughts and/or self-harm were recorded in only 6 of those 21 studies.

In Study 056, a patient allocated to the paroxetine treatment group committed suicide. However, the patient committed suicide before the start of active study medication. The patient's Screening (day –7) Visit was on 24 Mar 1990. The suicide was on 27 Mar 1990. Although randomised to the paroxetine treatment group, the patient had not taken paroxetine before the suicide.

In Study 097, one patient randomised to receive placebo and ECT treatment committed suicide by hanging 16 weeks after starting study medication.

In Study 338, there was one suicide attempt (described as severe) in the comparator (amitriptyline) group.

In Study 660, there were three suicide-related events reported as Serious AEs (SAEs). One was a report of suicidal ideation in a patient during the placebo run-in observation period. The other two events occurred when the patients were taking randomised study medication. They were a suicide attempt (intentional overdose) described as of moderate severity in a patient receiving paroxetine, and a suicide attempt (tranquiliser overdose) described as severe in a patient receiving placebo.

In Study 661, there was one report of suicidal ideation in a patient receiving placebo.

Finally, in Study 717, there were two SAEs reports of patients receiving 12.5mg/day paroxetine CR that had events that could be described as possibly suicide-related. One report was of emotional lability, the other was depression with emotional lability. Both events were described as severe, and described as probably unrelated to study medication.

In total, there were only nine adverse events relating to suicide, suicidal thoughts and/or self-harm in the 21 studies in adults, and of those 2 occurred before the patients had started randomised study medication. From the data available the incidence of suicide related adverse events in these 21 studies in adults was low. Approximately 0.14% (3/2127) in patients receiving paroxetine, 0.50% (3/597) in patients receiving placebo, and 0.12% (1/840) in patients receiving active comparators.

1.2.2.2. Study in adolescents

The safety data from Study 511, the French study in adolescents with unipolar depression, were included in the Marketing Authorisation Safety Update relating to paroxetine and data from Obsessive Compulsive Disorder, Social Anxiety Disorder / Social Phobia and Major Depressive Disorder studies in Children and Adolescents that was submitted in Europe in June 2003. The following text (in italics) was included in Module 2.7.4 Summary of Clinical Safety, Section 2.1.1.8, "Adverse Experiences from Other Clinical Sources"

This section summarizes paroxetine paediatric safety data from sources other than the clinical studies pivotal to this submission, i.e., data/reports obtained from published literature and post-marketing adverse event reports.

Controlled Studies

A double-blind, randomised, multicentre study conducted in France has been published comparing paroxetine and clomipramine in adolescents with severe major depression [Braconnier, 2003]. Patients were randomised to 20mg/day or 40mg/day of paroxetine or 75 mg or 150 mg of clomipramine for 8 weeks. Primary outcome measures were the Clinical Global Impression (CGI) Global Improvement Scale and the Montgomery and Asberg Depression Rating Scale (MADRS). Of the 121 patients randomised, 63 received

paroxetine and 58 received clomipramine. Based on intent-to-treat analysis both agents had similar efficacy: 65.1% and 59.3% of those receiving paroxetine and 48.3% and 58.2% of those receiving clomipramine were rated as responders on the MADRS and CGI scales, respectively. Study withdrawals were frequent in both groups (31% from paroxetine, 41% from clomipramine), and similar numbers of patients withdrew from each group because of adverse events (13 from clomipramine, 14 from paroxetine). Treatment emergent adverse experiences were reported by 86.0% of patients treated with clomipramine and 74.6% of patients treated with paroxetine. The proportion of patients with side effects (adverse experiences assessed by the investigators as probably related to treatment) was significantly higher with clomipramine than paroxetine (69.0% vs 49.2%, respectively; p = 0.027). Adverse experiences occurring in ³ 10% of subjects in any one treatment group are given in Table 20.

Table 20 Adverse Experiences Occurring in Greater than or equal to 10% of Patients in study by Braconnier et al (*J. Am. Acad. Child Adolesc. Psychiatry*, 2003,42(1):22-29.)

Adverse Experience	Paroxetine N = 63 n (%)	Clomipramine N = 58 n (%)
Suicidal act	8 (12.7)	7 (12.1)
Dizziness	4 (6.3)	20 (34.5)
Headache	11 (17.5)	14 (24.1)
Somnolence	5 (7.9)	6 (10.3)
Tremor	2 (3.2)	12 (20.7)
Dry Mouth	4 (6.3)	10 (17.2)
Nausea	7 (11.1)	14 (24.1)
Anxiety	19 (30.2)	10 (17.2)
Insomnia	7 (11.1)	16 (27.6)

The authors did not draw attention to the apparently high incidence of "suicidal act" observed in both treatment groups. However on discussing the limitations of their study , and in particular when making the point that the lack of a placebo control group prevents making any conclusion about the efficacy of paroxetine or clomipramine in adolescent depression, they say that the lack of a placebo control group was chosen by the investigators for ethical reasons. To quote the paper "most of them refused to have potentially suicidal adolescents with severe MDD on a placebo regimen". With the exception of "suicidal act", the adverse experiences profile reported on paroxetine was similar to that reported previously in other uses.

The risk of suicide-related adverse events was considerably higher in the adolescent population in Study 511 than in the 21 studies in adults. Study 511 was in patients with unipolar depression whereas a variety of indications including depression, OCD, Panic Disorder, Social Anxiety Disorder and PMDD were studied in the adult trials. However, restricting comparison to adult studies in depression, it is still apparent that the risk of suicide-related events in the adolescent population studied in Study 511 was indeed greater than that in the adult studies. It should be noted that the incidence of suicide acts

was very similar in adolescent patients treated with paroxetine or clomipramine, suggesting that the risk of such events in adolescents with depression is no greater in patients receiving paroxetine than other antidepressant drugs.

1.3. Conclusions

The 22 studies described previously as controlled studies not included in the central R&D aggregated database for a variety of practical reasons, have been reviewed, focussing on data relating to suicide, suicidal thoughts and self-harm. The data from the studies in adults support previous observations from studies on the central R&D aggregated database. From the available data, in the adult population studied, there was no increased risk of possibly suicide related events in patients receiving paroxetine compared to those receiving placebo.

The single study conducted in adolescents (Study 511) provided evidence of higher risk of possibly suicide-related adverse events in adolescents with depression, this data was provided to all EU agencies within the June 2003 paediatric safety update. Study 511 adds to that previous experience in that the similar incidences of such events in patients who received paroxetine and clomipramine suggests that the risk of suicide-related adverse events is no greater in patients receiving paroxetine than other antidepressants.