5. QUESTION 5: CRITICAL ASSESSMENT OF SELF-HARM, SUICIDAL BEHAVIOUR AND HOSTILITY DATA

The MAH should provide a critical assessment of these data and their significance.

Response

5.1. Introduction

The responses to Questions 2 and 3 provide data on the risk of possibly suicide-related, self-harm and hostility events in adults, adolescents and children treated with paroxetine, as well as identifying the risk factors associated with these events. The responses to these questions encompass data from paroxetine clinical trials, post-marketing reports (including spontaneous and consumer reports), healthy volunteer data, observational studies and an extensive review of the literature. The main findings presented in response to Questions 2 and 3 are critically reviewed in this section.

5.2. Self-harm and suicidal behaviour in adults

5.2.1. Clinical studies

In order to respond to Question 2, which asked for data on the risk of possibly suicide-related and self-harm events, data from the adult studies within the GSK central R&D aggregated database were investigated in the following ways:

- the incidence of emergent suicidal ideation was assessed based on the suicide item (Item 3) of the Hamilton Depression Rating Scale (HAM-D). Emergent suicidal ideation was defined as a baseline score of 0 or 1 on Item 3 of the HAM-D changing to a post-baseline score of ≥3.
- the change from baseline in two measures of suicidality (Item 3 of the HAM-D and Item 10 of the Montgomery Asberg Depression Rating Scale (MADRS)) was assessed.
- the incidence of possibly suicide-related and self-harm adverse events was assessed using pre-defined searching algorithms run across two populations - the "on-therapy" population and the "on-therapy plus 30 days" population.

These three types of analyses were run across the adult clinical trial data within the GSK central R&D aggregated database, and thus were employed across data from over 24,000 adult patients from placebo-controlled and active-controlled paroxetine studies.

5.2.1.1. Controlled studies

The main findings from the adult placebo-controlled and active-controlled studies, as presented in detail in the response to Question 2, are summarised in the following bullet points:

- The adult placebo-controlled dataset comprised a total of 14,289 patients; 8,481 patients exposed to paroxetine and 5,808 to placebo.
- The adult active-controlled dataset comprised a total of 11,491 patients; 6,522 patients exposed to paroxetine and 4,969 to active comparators, including other SSRIs, tricyclics, tetracyclics, benzodiazepines and other antidepressant medications.
- In both the placebo-controlled and the active-controlled adult studies, there was no evidence of emergent suicidal ideation (based on Item 3 of the HAM-D) in the paroxetine treatment groups compared to the placebo / active comparator groups.
- In both the placebo-controlled and the active-controlled adult studies, a statistically significant treatment benefit with paroxetine was seen in the change from baseline of Item 3 of the HAM-D.
- In the placebo-controlled adult studies, a statistically significant treatment difference in favour of paroxetine was seen in the change from baseline of Item 10 of the MADRS. In the active-controlled adult studies, there was no significant difference in the change from baseline in Item 10 of the MADRS between the paroxetine treatment group and the active comparator group.
- In the placebo-controlled adult studies, there was no difference in the incidence of possibly suicide-related and self-harm events between the paroxetine treatment group and the placebo group, in both the "on-therapy" and the "on-therapy plus 30 days" populations.
- In the active-controlled adult studies, there was a lower incidence of possibly suicide-related and self-harm events in the paroxetine treatment group compared to the active comparator group overall. This was the case for both the "on-therapy" and the "on-therapy plus 30 days" populations, although the difference only reached statistical significance for on-therapy possibly suicide-related events.

Clinically the data summarised here and presented in this response are very important and highly relevant to the populations being treated. Assessment of suicidal ideation by use of specific items from well-validated and utilised scales is more sensitive than would be expected from the use of routine adverse event monitoring. In this way the data is helpful in understanding the efficacy of different treatments in improving suicidal behaviour if present at baseline and looking for emergent suicidal ideation.

No compelling evidence to link suicidality/ self harm with the use of paroxetine in adults was found from this comprehensive review.

Available data show efficacy of paroxetine in ameliorating baseline suicidal ideation and intent and demonstrate a clinically important benefit over active comparators.

5.2.1.2. Uncontrolled studies

The findings from the adult uncontrolled studies are presented in detail in the response to Question 2. Compared to the controlled studies these are less easy to interpret given the nature of their design. The main finding was that similar incidence rates of possibly suicide-related and self-harm events were seen in the uncontrolled adult studies compared

to the paroxetine treatment arms of the adult placebo-controlled and active-controlled studies. This is reassuring and adds further validity to the controlled data findings.

5.2.2. Identification of risk factors for self-harm and suicidal behaviour from the clinical trial data

The clinical trial data did not provide any evidence to suggest that paroxetine treatment increases the risk of suicidal behaviour or self-harm in adults. Therefore, the risk factor analysis focused on identifying any subgroups of adult patients who might be at greater or reduced risk of such events. The results of the risk factor analyses performed are presented in detail in the response to Question 3 (see Question 3, Section 3.2) but the main findings are summarised in the following bullet points:

- Young adults have an increased risk of possibly suicide-related and self-harm events, irrespective of treatment. Compared to placebo-treated patients, this effect appears to be heightened among patients treated with antidepressants. However, patients treated with paroxetine were at a lower risk compared to those treated with other SSRIs and other classes of antidepressants.
- Patients with baseline suicidal ideation were less likely to experience possibly suicide-related and self-harm events if treated with paroxetine than if treated with placebo.
- Several other factors (e.g. suicidal history, prior psychotropic medication) were identified as being contributors to an increased risk of possibly suicide-related and self harm events, irrespective of whether patients were treated with paroxetine.

5.2.3. Post-marketing reports (including spontaneous and consumer reports)

The post-marketing data from the GSK clinical safety database contains reports of adverse events from clinical trials (mainly serious adverse events), post-marketing surveillance (PMS) studies, spontaneous/unsolicited notifications, literature and regulatory sources. The main results from the post-marketing data, as presented in detail in the responses to Questions 2 and 3, are summarised in the following bullet points:

- Up until 31st May 2003 the database contained a total of 42,844 reports relating to paroxetine, 41,472 of which concerned adults or patients of unspecified age.
- There was a total of 1,413 self-harm / suicidal behaviour reports relating to adults or patients of unspecified age, of which 306 reported a completed suicide, 726 reported an attempted suicide or an act of self-harm and 381 reported suicidal or self-harming ideation.
- Reporting of self-harm / suicidal behaviour events increased abruptly in 2002. Product liability litigation and media coverage, particularly in the US and the UK, could have contributed to this abrupt rise in the reporting of such events.
- A higher proportion of young adults were reported to have experienced self-harm/suicidal behaviour events compared to the proportion of young adults who were reported to have experienced other events.

- A higher proportion of male patients were reported to have experienced self-harm/suicidal behaviour events compared to the proportion of male patients who were reported to have experienced other events.
- A higher proportion of the following groups of patients reported self-harm/suicidal behaviour events compared to the proportion of the same groups of patients who reported other events: those who were being treated for depression, those with previous psychiatric history and those who concomitantly used other psychotropic medications.
- The majority of self-harm/suicidal behaviour events occurred within the first month of paroxetine therapy, and of those events that occurred within the first month, the majority occurred within the first two weeks of therapy.
- In summary, this data suggests that the reporting of self-harm/suicidal behaviour events is significantly influenced by the epidemiology and nature of the depressive conditions requiring anti-depressant treatment.
- Self-harm/suicidal behaviour events were found not to be dose related.

5.2.4. Healthy volunteer studies

Adverse event data from a total of 1,716 healthy adult volunteers exposed to paroxetine was examined for possibly suicide-related and self-harm events. No cases of possibly suicide-related or self-harm events were reported within this dataset.

As opposed to the depressed population, this is not surprising as the adult volunteers were not suffering from a known psychiatric disorder and should not therefore be at increased risk of suicidal behaviour and/or self-harm. It has been proposed, because these studies can remove underlying disease as a contributory factor, that healthy volunteer studies are useful in generation of evidence of a causal link between treatment and suicide-related events.

The lack of any cases of suicide-related or self-harm events seen in this dataset appears to further help refute this causal link hypothesis.

5.2.5. Observational studies and literature review

Data from observational studies, including data from a Prescription Event Monitoring (PEM) study, are presented in response to Question 2 (see Question 2, Section 2.4). Overall, these studies provided no evidence to suggest that the incidence rate of events related to self-harm / suicidal behaviour in patients treated with paroxetine is any higher than the rate in patients treated with other antidepressant medications.

A review of the literature did not reveal any randomised clinical trials that provide evidence of an increased incidence of suicidality amongst paroxetine treated patients compared to placebo. To the contrary, there is evidence in the literature of a decreased incidence of suicidality in paroxetine treated patients.

5.2.6. Overall summary of self-harm and suicidal behaviour in adults

From the range of data sources that have been reviewed, there is no evidence to suggest that there is an increased risk of self-harm or suicidal behaviour in adults treated with paroxetine. In fact, the clinical trial data demonstrated that paroxetine showed a greater improvement in measures of suicidality (Item 3 of the HAM-D and Item 10 of the MADRS) compared to placebo and compared to other antidepressant medications. The clinical trial data also demonstrated that paroxetine was beneficial in patients with baseline suicidal ideation; patients with baseline suicidal ideation were less likely to experience possibly suicide-related and self harm events if treated with paroxetine than if treated with placebo. And finally, the clinical trial data also revealed a lower incidence of possibly suicide-related and self-harm events in the paroxetine treatment group compared to other antidepressant medications.

These data strongly refute the suggestion that treatment with paroxetine may increase the risk of self-harm and suicidal behaviour in adults.

5.3. Hostility in adults

5.3.1. Clinical studies and identification of risk factors for hostility from the clinical trial data

The incidence of hostility adverse events from the adult studies within the GSK central R&D aggregated database was assessed using a pre-defined searching algorithm. This algorithm was run across two populations - the "on-therapy" population and the "on-therapy plus 30 days" population.

The findings from the adult placebo-controlled, adult active-controlled and adult uncontrolled studies are presented in detail in the response to Question 2. The main findings were as follows:

- In adults treated with paroxetine, there was a low incidence of hostility events.
- In the controlled studies there was no difference in the incidence of hostility adverse events between the paroxetine treatment group and the placebo / active comparator group in both the "on-therapy" and the "on-therapy plus 30 days" populations.
- Similar incidence rates of hostility events were seen in the uncontrolled adult studies compared to the paroxetine treatment arms of the adult placebo-controlled and active-controlled studies.

Therefore, the data from the paroxetine clinical trial database, which includes data from more than 24,000 adult patients from placebo-controlled and active-controlled studies, does not suggest any link between paroxetine treatment and hostility in adults. Furthermore, no particular subgroup of adults was identified as being at risk of hostility events with paroxetine treatment.

5.3.2. Post-marketing reports (including spontaneous and consumer reports)

The post-marketing data from the GSK clinical safety database contains reports of adverse events from clinical trials (mainly serious adverse events), post-marketing surveillance (PMS) studies, spontaneous/unsolicited notifications, literature and regulatory sources. The main results from the post-marketing data, as presented in detail in the responses to Questions 2 and 3, are summarised in the following bullet points:

- Up until 31st May 2003 the database contained a total of 42,844 reports relating to paroxetine, 41,472 of which concerned adults or patients of unspecified age.
- There was a total of 685 reports of hostility relating to adults or patients of unspecified age, of which 309 reported physical acts of aggression and violence (36 of which reported murder), 325 reported non-physical or unspecified aggression (including verbal) and 51 reported hostile or aggressive ideation.
- Reporting of hostility events increased abruptly in 2001 and 2002. Product liability litigation and media coverage, particularly in the US and the UK, could have contributed to this abrupt rise in the reporting of such events.
- A higher proportion of young adults were reported to have experienced hostility events compared to the proportion of young adults who were reported to have experienced other events.
- A higher proportion of male patients were reported to have experienced hostility events compared to the proportion of male patients who were reported to have experienced other events.
- The majority of hostility events occurred within the first month of paroxetine therapy, and of those events that occurred within the first month, the majority occurred within the first two weeks of therapy.
- Hostility events were found not to be dose related.

5.3.3. Healthy volunteer studies

Adverse event data from a total of 1,716 healthy adult volunteers exposed to paroxetine was examined for hostility events and just 3 cases were identified. All 3 cases were reports of aggression and all resolved without further incident. Such events are occasionally seen across Phase I studies, and are attributed to the necessity to confine volunteers to a clinical unit for several days in some studies.

5.3.4. Observational studies and literature review

Data from observational studies, including data from a Prescription Event Monitoring (PEM) study, are presented in response to Question 2 (see Question 2, Section 2.4). Overall, there was a low reporting of hostility-related events. In the PEM study, there was no particular clustering of events in the first month of therapy that might be suggestive of a drug (or disease) related event.

The main conclusion from the review of the literature was that there does not seem to be any causal link between aggression/hostility and any SSRIs, including paroxetine. To the contrary, the published randomised controlled studies suggest that SSRIs reduce the level of hostility in adults.

5.3.5. Overall summary of hostility in adults

From the range of data sources that have been reviewed, there is no evidence to suggest that there is an increased risk of hostile/aggressive behaviour in adults treated with paroxetine.

5.4. Self-harm and suicidal behaviour in children and adolescents

5.4.1. Clinical studies and identification of risk factors for self-harm and suicidal behaviour from the clinical trial data

In order to respond to Question 2, which asked for data on the risk of possibly suicide-related and self-harm events, data from the paediatric placebo-controlled studies within the GSK central R&D aggregated database were investigated in the following three ways:

- the incidence of emergent suicidal ideation was assessed based on the suicide item (Item 3) of the Hamilton Depression Rating Scale (HAM-D). Emergent suicidal ideation was defined as a baseline score of 0 or 1 on Item 3 of the HAM-D changing to a post-baseline score of ≥3.
- the change from baseline in two measures of suicidality (Item 3 of the HAM-D and Item 10 of the Montgomery Asberg Depression Rating Scale (MADRS)) was assessed.
- the incidence of possibly suicide-related and self-harm adverse events was assessed using pre-defined searching algorithms run across two populations - the "on-therapy" population and the "on-therapy plus 30 days" population.

The main findings from the paediatric placebo-controlled studies are presented in detail in the responses to Questions 2 and 3, and are summarised in the following bullet points:

- The paediatric placebo-controlled dataset comprised a total of 1,385 children and adolescents; 738 exposed to paroxetine and 647 to placebo.
- The incidence of emergent suicidal ideation was 3.2% in the paroxetine treatment group and 0.7% in the placebo group. However, in order to assess the clinical significance of these incidence rates, it is important to consider that they reflect just five cases in the paroxetine group and one in the placebo group.
- There was no significant difference in the change from baseline in Item 3 of the HAM-D or in Item 10 of the MADRS between the paroxetine treatment group and the placebo group.
- There were no completed suicides in the paediatric placebo-controlled studies.

- The incidence of possibly suicide-related and self-harm events was greater in paroxetine treated patients than in patients who received placebo, primarily in adolescents with major depressive disorder.
- Risk factors for possibly suicide-related and self-harm events identified in the paediatric population included female gender, baseline suicidal ideation and baseline disease severity, but all were irrespective of treatment.
- There is insufficient active comparator data in the paediatric population to determine whether the effects are specific to paroxetine or are common to other antidepressants.

Children and adolescents being treated for paediatric depression are at higher risk of suicidality/self-harm events, with adolescents at greatest risk. This is borne out by the data presented here. The events in both treatment groups were predominantly in adolescent patients with depression. The number of cases reported was however small and with such small numbers and with events that may have many complex contributing factors it is difficult to be certain that the effect is attributable to drug treatment. It is possible that confounding factors may have contributed to this apparent difference. Indeed it would take only a small imbalance in confounding factors between treatment groups to remove the apparent difference between the groups.

Possible confounding factors have been assessed as far as possible in the paediatric patients for whom possibly suicide-related AEs have been reported. However, there can be many factors that can contribute to a patient experiencing suicidal behaviour. Risk factors for suicide and attempted suicide among young people that have been identified in the literature include social and educational disadvantage, childhood and family adversity (which may include family violence, family arguments, not living with both parents, low level of parental support, frequent geographical moving, exposure to sexual abuse), psychopathology, and exposure to stressful life events and circumstances. Frequently, suicidal behaviours in young people appear to be a consequence of adverse life experiences and relationship conflicts in which multiple risk factors from these domains combine to increase risk of suicidal behaviour. While we have been able to assess our paediatric clinical trial database for some risk factors, such as previous suicidal behaviour, presence of suicidal ideation at baseline and presence of comorbid anxiety, which did not affect the treatment effect, there are others for which we do not have the information to assess whether they may have been contributing factors in our study population or not. Such information is not collected in our clinical trial programmes, nor would it be feasible to collect information related to every possible confounder in ongoing or future trials, as they are individually determined. Although unmeasured confounders should also have been balanced by randomisation, without knowing such information on important risk factors for suicidal behaviour in children, especially given the small numbers involved, makes it difficult to draw definitive conclusions.

5.4.2. Post-marketing reports (including spontaneous and consumer reports)

The post-marketing data from the GSK clinical safety database contains reports of adverse events from clinical trials (mainly serious adverse events), post-marketing surveillance (PMS) studies, spontaneous/unsolicited notifications, literature and regulatory sources. The main results from the post-marketing data, as presented in detail in the responses to Questions 2 and 3, are summarised in the following bullet points:

- Up until 31st May 2003 the database contained a total of 42,844 reports relating to paroxetine, 1,372 of which concerned paediatric patients (<18 years).
- There was a total of 126 self-harm / suicidal behaviour reports relating to paediatric patients, of which 15 reported a completed suicide, 88 reported an attempted suicide or an act of self-harm and 23 reported suicidal or self-harming ideation.
- Reporting of self-harm / suicidal behaviour events increased abruptly in 2002. Product liability litigation and media coverage, particularly in the US and the UK, could have contributed to this abrupt rise in the reporting of such events.
- A higher proportion of adolescents (12-17 years) were reported to have experienced self-harm/suicidal behaviour events compared to the proportion of adolescents who were reported to have experienced other events.
- A higher proportion of female paediatric patients were reported to have experienced self-harm/suicidal behaviour events compared to the proportion of female paediatric patients who were reported to have experienced other events.
- A higher proportion of the following groups of paediatric patients reported self-harm/suicidal behaviour events compared to the proportion of the same groups of patients who reported other events: those who were being treated for depression and those with previous psychiatric history.

5.4.3. Overall summary of self-harm and suicidal behaviour in children and adolescents

The database of paediatric studies was not as large as for adult studies; therefore the analyses reported for paediatric patients did not have the same power as those conducted in the adult population. Furthermore limited active controls were available for this review of the safety of paroxetine in the paediatric population. Apart from the clinical trial program, there are also limited sources of additional information.

There are many factors that can contribute to a patient experiencing suicidal behaviour.

A numerically increased incidence of suicide-related adverse events is reported in depressed adolescents. The clinical significance of this finding is far from clear given the potential for confounders and the small numbers involved and must be weighed against the potential for any individual to benefit from therapy. Events occurring on-therapy were small in number and generally mild to moderate in intensity.

The incidence of possibly suicide-related events and self-harm was low among OCD and SAD patients. Although in MDD there is a signal (with the potential for confounding factors) there is no compelling evidence that paroxetine is not safe, with regards to emergent suicidality, in OCD and SAD paediatric patients.

5.5. Hostility in children and adolescents

5.5.1. Clinical studies and identification of risk factors for hostility from the clinical trial data

The incidence of hostility adverse events from the paediatric studies within the GSK central R&D aggregated database was assessed using a pre-defined searching algorithm. This algorithm was run across two populations - the "on-therapy" population and the "on-therapy plus 30 days" population. The findings are presented in detail in the responses to Questions 2 and 3, but the main findings were as follows:

- In the paediatric population overall, paroxetine was associated with an increased risk of hostility compared to placebo.
- This increased risk of hostility was mainly seen in patients with OCD and in children under the age of 12 years.
- There is insufficient active comparator data in the paediatric population to determine whether this effect is specific to paroxetine or is common to other antidepressants.

5.5.2. Post-marketing reports (including spontaneous and consumer reports)

The post-marketing data from the GSK clinical safety database contained reports of adverse events from clinical trials (mainly serious adverse events), post-marketing surveillance (PMS) studies, spontaneous/unsolicited notifications, literature and regulatory sources. The main results from the post-marketing data, as presented in detail in the responses to Questions 2 and 3, are summarised in the following bullet points:

- Up until 31st May 2003 the database contained a total of 42,844 reports relating to paroxetine, 1,372 of which concerned paediatric patients (<18 years).
- There was a total of 106 reports of hostility relating to paediatric patients, of which 57 reported physical acts of aggression and violence (12 of which reported murder), 44 reported non-physical or unspecified aggression (including verbal) and 5 reported hostile or aggressive ideation.
- Reporting of hostility events increased abruptly in 2001 and 2002. Product liability litigation and media coverage, particularly in the US and the UK, could have contributed to this abrupt rise in the reporting of such events.
- A higher proportion of children (up to 11 years) were reported to have experienced hostility events compared to the proportion of children who were reported to have experienced other events.

- A higher proportion of male paediatric patients were reported to have experienced hostility events compared to the proportion of male paediatric patients who were reported to have experienced other events.
- A higher proportion of the following groups of paediatric patients reported hostility events compared to the proportion of the same groups of patients who reported other events: those with previous psychiatric history and those who concomitantly used other psychotropic medications.

5.5.3. Overall summary of hostility in children and adolescents

Hostility covers a range of behaviours ranging in clinical importance from feeling angry to violent behaviour. Hostility related emergent events in the paediatric population appear to be increased by treatment with paroxetine, mainly in children (<12years) with OCD. These events were most frequently not serious and treatment with paroxetine was continued in the majority of cases. This is not surprising, as symptoms such as irritability and hostility are a relatively frequent clinical feature of psychiatric disturbance in children and adolescents, especially in OCD. When it was necessary to stop paroxetine, other concomitant side effects had also been observed. Serious adverse events of emergent hostility were seen in very small numbers of both paroxetine and placebo patients.

5.6. Overall conclusion

At the end of this comprehensive review of extensive data from a variety of sources, GSK concludes that there is no compelling scientific evidence that paroxetine increases the risk of emergent suicidal or hostility related events in adults. In fact some evidence exists that paroxetine reduces the risk of suicidality in adults, especially compared to other anti-depressants. This review also failed to identify any factor that could increase this risk in particular sub-populations in adults. We also believe that the evidence to the contrary, which has been proposed by some sources external to GSK, is methodologically flawed and scientifically weak. The current prescribing information for paroxetine in adults is fully supported by the comprehensive review that has been conducted and does not require any change.

Less clear-cut conclusions can be drawn at the end of the review of paediatric data. The statistical power of analyses conducted on the paediatric data was lower than that of the adult analyses, in view of the relatively small size of the database, and the relatively low number of events.

Nevertheless a signal has emerged, indicating that paroxetine may increase the risk of emergent suicidal behaviour, predominantly in depressed adolescents.

A signal was also seen for emergent hostile behaviour, particularly in children with OCD and especially in younger children less than 12 years of age.

The data analysed in this review did not enable a definitive confirmation of these findings nor any understanding of their likely physiopathological basis.

Further research (see Question 11) is necessary to try and better ascertain the risk posed by paroxetine in children/adolescents and its causes, and then to allow a better definition of possible strategies to minimise the risk. Emergent suicide related events were almost exclusively observed in depressed patients, and hostility related events were in the majority of instances not severe and in few instances required drug discontinuation. Based on these findings, data does not support the use of paroxetine in the treatment of children and adolescents with Major Depressive Disorder. However in those new indications with proven efficacy (paediatric SAD and OCD) paroxetine could still prove to be a valuable therapeutic tool in the hands of clinicians. We believe that risks could be adequately minimised in the paediatric population by adding more explicit warnings in the data sheet as outlined in Question 10.