

4. QUESTION 4

Provide time to onset data from clinical trials as survival plots.

Response

4.1. Time to onset of possibly suicide-related events presented as survival plots

Survival plots for possibly suicide-related events in adult placebo-controlled trials, adult active control trials, and paediatric placebo-controlled trials are shown on the following pages in [Figures 4.1 – 4.3](#). (Data source: Appendix 1, [Figures 1.01 – 1.03](#)). Corresponding survival plots including 95% confidence intervals are included as [Figures 4.4 – 4.6](#). (Data source: Appendix 1, [Figures 1.01a – 1.03a](#)).

Please Note: It may be easier to view the enclosed graphs in the electronic CD version of this submission as they might be easier to review in colour.

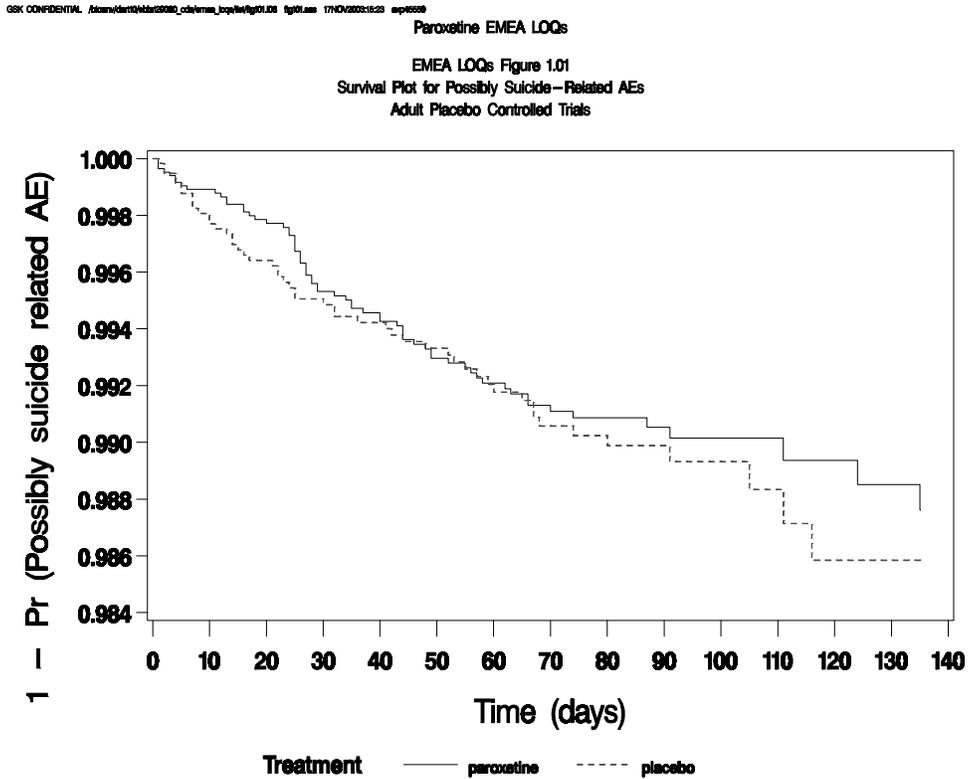
In the adult placebo-controlled studies ([Figure 4.1](#) and [Figure 4.4](#)), the hazard ratio of 0.83, 95% C.I [0.58, 1.19] indicates that in these studies at any given time, the risk of a possibly suicide-related event was marginally less likely on paroxetine than placebo, but that the difference in risk was not statistically significant.

In the adult active control trials ([Figure 4.2](#) and [Figure 4.5](#)), the hazard ratio of 0.66, 95% C.I [0.46, 0.94] indicates that under the assumption of proportional hazards, at any given time, the risk of a possibly suicide-related event was two-thirds as likely on paroxetine as on active comparator treatment.

In the paediatric placebo-controlled trials ([Figure 4.3](#) and [Figure 4.6](#)), the hazard ratio of 2.20, 95% C.I. [0.92, 5.26] indicates that at any given time, the risk of a possibly suicide-related event was over twice as likely on paroxetine as on placebo.

In all three cases, there is no compelling evidence to reject the assumption of proportional hazards. In the adult placebo-controlled trials population, the hazards appear to converge and then diverge again, but given the degree of uncertainty around these estimates, this is probably more likely to be a representation of equal hazards in the two groups rather than any systematic deviation from proportional hazards.

**Figure 4.1 Survival Plot for Possibly Suicide-Related Events
Adult Placebo-Controlled Trials**



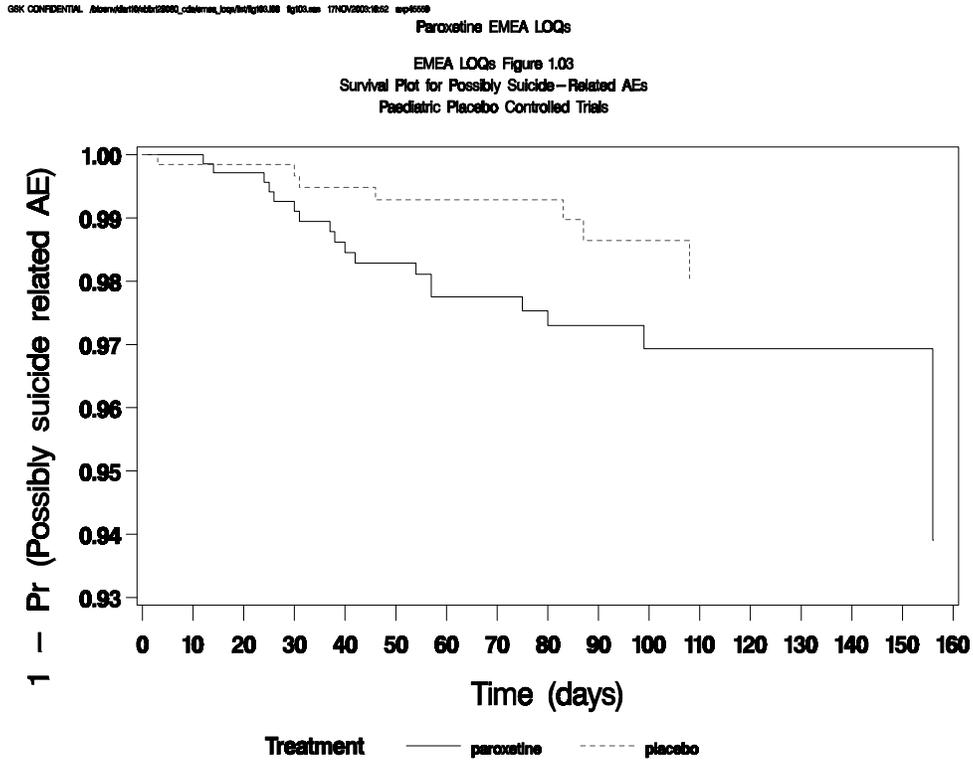
Log-rank test P=0.31

Hazard ratio=0.83, 95% C.I. [0.58, 1.19]

Hazard ratio calculated as the risk on paroxetine compared to placebo.

Test of treatment by time interaction in PH (Proportional Hazards) model P=0.13

**Figure 4.3 Survival Plot for Possibly Suicide-Related Events
Paediatric Placebo-Controlled Trials**



Log-rank test P=0.07.

Hazard ratio=2.20 95% C.I. [0.92, 5.26]

Hazard ratio calculated as the risk on paroxetine compared to placebo.

Test of treatment by time interaction in PH model P=0.68

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Figure 4.4 Survival Plot for Possibly Suicide-Related Events with 95% C.I Adult Placebo-Controlled Trials

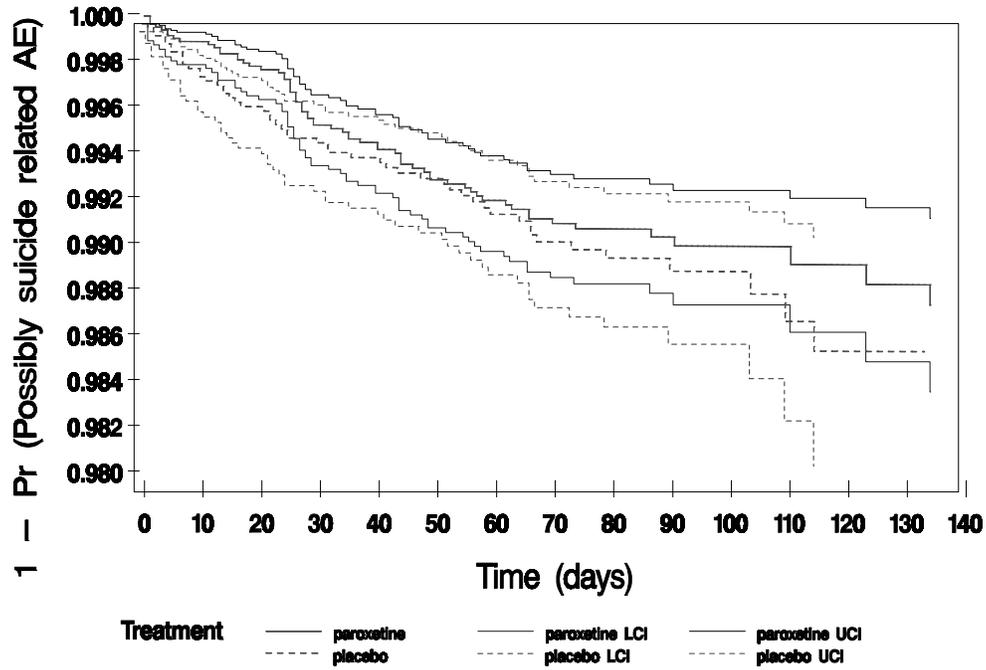
GGK CONFIDENTIAL /obsrv/ent/046b/2020_cde/emas_lcp/fig/01a.00 fig/01a.00 17/NOV/2022/16:52 ep/6529

Paroxetine EMEA LOQs

EMEA LOQs Figure 1.01a

Survival Plot for Possibly Suicide-Related AEs with 95% C.I.

Adult Placebo Controlled Trials



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Figure 4.5 Survival Plot for Possibly Suicide-Related Events with 95% C.I. Adult Active-Control Trials

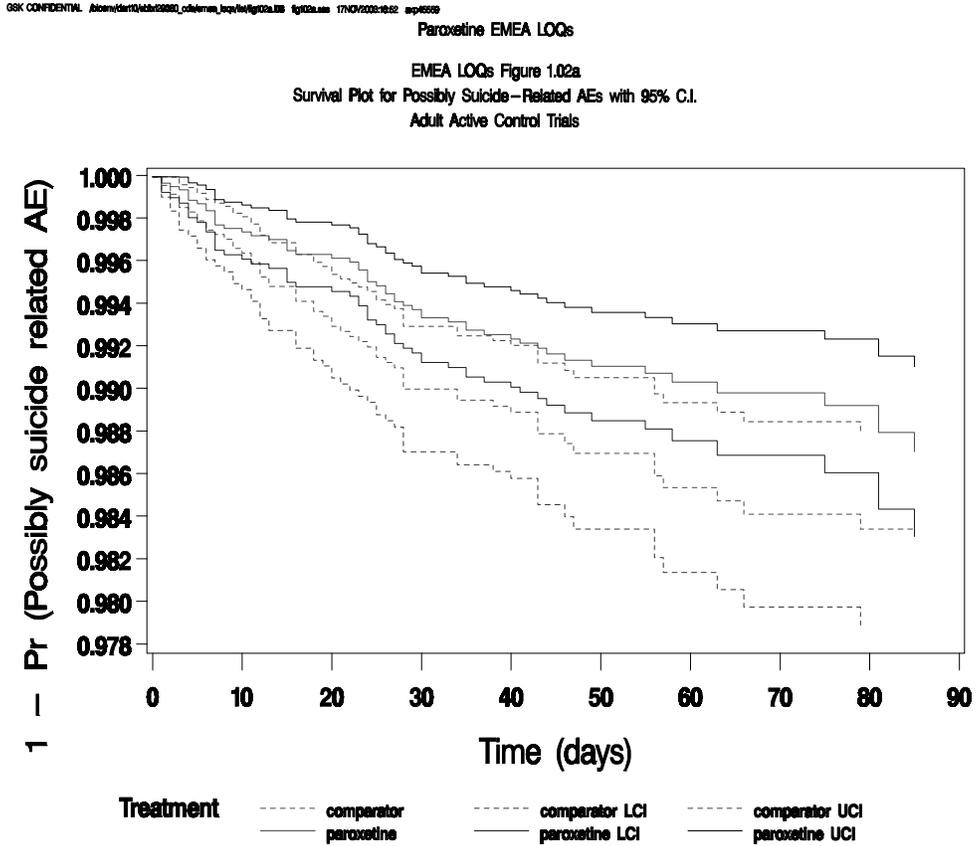
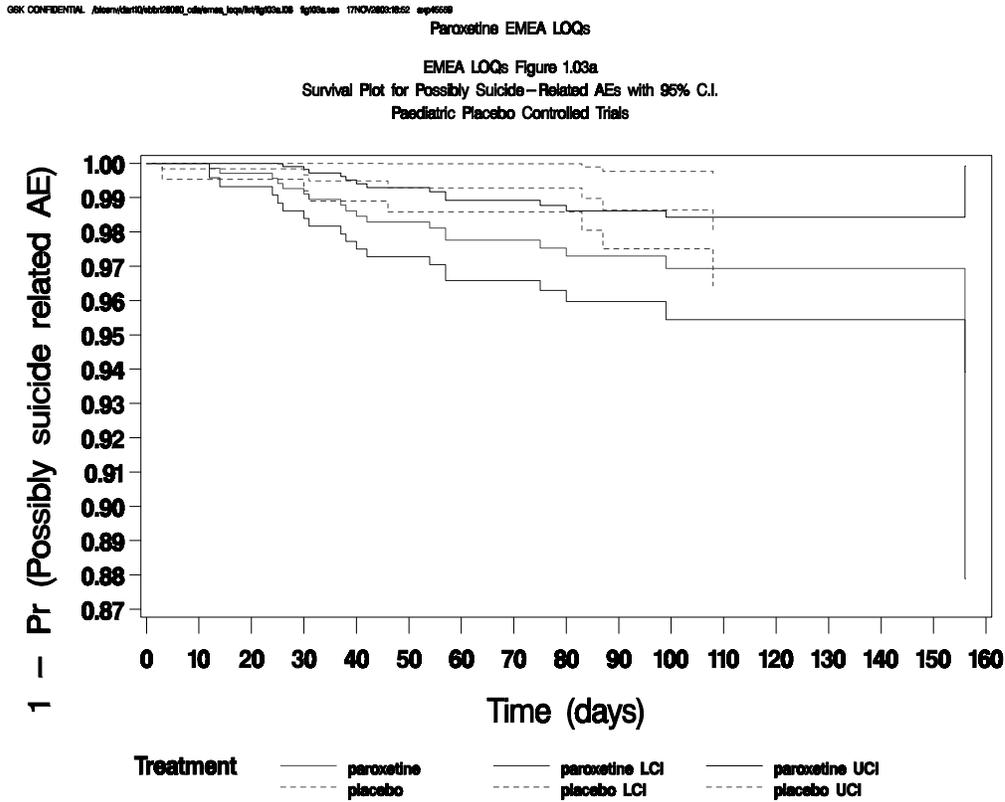


Figure 4.6 Survival Plot for Possibly Suicide-Related Events with 95% C.I. Paediatric Placebo-Controlled Trials



4.2. Conclusion

The survival plots indicate that at any given time, the risk of a possibly suicide-related event in adults taking paroxetine was similar to the risk on placebo and less than the risk on active comparator treatment. In paediatric studies, at any given time, patients were more likely to have a possibly suicide-related event on paroxetine than on placebo.