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Results for review of data about "suicide attempts" in 1991 report

Prepared by:

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Date: 6th February 2002

A. Placebo controlled trials

1. Identify all placebo-controlled trials used in original NDA, including paroxetine and placebo data from three-arm trials. Studies PAR-04 and PAR-014 will be excluded by virtue of their design (PAR-04 is an extension of PAR-03, and encompasses some element of crossover of treatments between the two studies; PAR-014 is described as a placebo-controlled trial in the study title, but is more accurately considered as uncontrolled). A footnote will be provided to confirm the studies included.
2. Confirm denominators for the subset of patients defined by point 1.
3. Confirm list of PIDs with events that were included in the 1991 FDA submission.
4. Exclude events outside the "On-Therapy plus 30 Days Post Therapy" window. Only the on-therapy phase will be included for patients continuing into an extension phase. Events occurring during an extension phase are captured in section C analysis. (Note: on this basis events occurring during placebo run-in phases are excluded.)
5. Identify by footnote any patients excluded through point 4, that were part of the list of patients with events in the 1991 FDA submission.
6. Calculate PYE for all patients, and calculate rate of patients with event relative to exposure. Exposure is calculated only for the period on-therapy, i.e. the 30-day post-therapy window is not used in calculating exposure.
7. The hypothesis of no association between treatment and incidence of "suicide attempt" will be tested using Fisher's exact test (two-tailed). Statistical significance will be assessed at the 5% level.
8. The number of patients attempting suicide relative to PYE (incidence density) will be analysed using SAS[®] PROC GENMOD. Should the frequency of suicides in either treatment group be too low for the model to converge to precise estimates, the Wilcoxon-Gehan exact test for right censored data will be employed from STATXACT[®] version 3.
9. Refer back to original Oracle tables, e.g. paroxetine_uspat.st@usarc7.
10. Provide a cell index listing patients with the event in both treatment groups.

	Paroxetine	Placebo	P-value
n/N (%)	5/921 (0.5%)	1/554 (0.2%)	0.42
PYE	108	51	
n/PYE (rate relative to exposure)	0.05	0.02	0.43

† in both cases above, n refers to the number of patients with the event

Five patients with attempted suicide have been excluded from the figures above for the placebo group because they occurred during the placebo run-in phase (1 09 021, 1 46 010, 7119 011, 7119 071, 7119 118).

B. Active control trials

1. Identify all active-controlled trials used in original NDA, including paroxetine and active control data from three-arm trials. Study PAR-04 will be excluded by virtue of its design (PAR-04 is an extension of PAR-03, and encompasses some element of crossover of treatments between the two studies). A footnote will be provided to confirm the studies included.
2. Confirm denominators for the subset of patients defined by point 1.
3. Confirm list of PIDs with events that were included in the 1991 FDA submission.
4. Exclude events outside the "On-Therapy plus 30 Days Post Therapy" window. Only the on-therapy phase will be included for patients continuing into an extension phase. Events occurring during an extension phase are captured in section C analysis. (Note: on this basis events occurring during placebo run-in phases are excluded.)
5. Identify by footnote any patients excluded through point 4, that were part of the list of patients with events in the 1991 FDA submission.
6. Calculate PYE for all patients, and calculate rate of patients with event relative to exposure. Exposure is calculated only for the period on-therapy, i.e. the 30-day post-therapy window is not used in calculating exposure.
7. The hypothesis of no association between treatment and incidence of "suicide attempt" will be tested using Fisher's exact test (two-tailed). Statistical significance will be assessed at the 5% level.
8. The number of patients attempting suicide relative to PYE (incidence density) will be analysed using SAS PROC GENMOD. Should the frequency of suicides in either treatment group be too low for the model to converge to precise estimates, the Wilcoxon-Gehan exact test for right censored data will be employed from STATXACT version 3.
9. Refer back to original Oracle tables, e.g. paroxetine_uspat.st@usarc7.
10. Provide a cell index listing patients with the event in both treatment groups.

	Paroxetine	Active Control	P-value
n/N (%)	12/1096 (1.1%)	11/1063 (1.0%)	1.00
PYE	136	120	
n/PYE (rate relative to exposure)	0.09	0.09	0.93

† in both cases above, n refers to the number of patients with the event

Two patients have been excluded from the count of events in this table; 03.006.088 (Active Control group) because the event occurred in the uncontrolled extension phase, and 1 13 010 (paroxetine group) because the event occurred in an open label extension.

C. All Paroxetine Data

1. Include data from all studies, both controlled and uncontrolled, including extension phases. A footnote will be provided to confirm the studies included.
2. Confirm denominators for the subset of patients defined by point 1.
3. Confirm list of PIDs with events that were included in the 1991 FDA submission.
4. Exclude events outside the "On-Therapy plus 30 Days Post Therapy" window. (Note: on this basis events occurring during placebo run-in phases are excluded.)
5. Identify by footnote any patients excluded through point 4, if any, that were part of the list of patients with events in the 1991 FDA submission.
6. Calculate PYE for all patients, and calculate rate of patients with event relative to exposure. Exposure is calculated only for the period on-therapy, i.e. the 30-day post-therapy window is not used in calculating exposure.
7. Refer back to original Oracle tables, e.g. paroxetine_uspat.st@usarc7.
8. Provide a cell index listing patients with the event in both treatment groups.

	Paroxetine
n/N (%)	40/2963 (1.3%)
PYE	1008
n/PYE (rate relative to exposure)	0.04

† in both cases above, n refers to the number of patients with the event

Appendix A Study Population

Protocol Title	Section A	Section B	Section C
STUDY 001	X		X
STUDY 002	X		X
STUDY 003	X	X	X
STUDY 004			X
STUDY 005			X
STUDY 006		X	X
STUDY 007	X	X	X
STUDY 009	X		X
MDUK04 [REDACTED]		X	X
MDUK05 [REDACTED]			X
MDUK06 [REDACTED]	X		X
MDUK07 [REDACTED]	X	X	X
MDUK09 [REDACTED]	X		X
MDUK12 [REDACTED]	X	X	X
MDUK13 [REDACTED]		X	X
MDUK14 [REDACTED]			X
MDUK20 [REDACTED]		X	X
MDUK22 [REDACTED]		X	X
MDUK24 [REDACTED]			X
MDUK25 [REDACTED]		X	X
MDUK26 [REDACTED]		X	X
MDUK27 [REDACTED]		X	X
MDUK28 [REDACTED]		X	X
MDUK29 [REDACTED]		X	X
MDUK30 [REDACTED]		X	X
MDUK32 [REDACTED]		X	X
MDUK34 [REDACTED]			X
MDUK35 [REDACTED]		X	X
MDUK37 [REDACTED]			X
MDUK38 [REDACTED]		X	X
MDUK40 [REDACTED]			X
MDUK41 [REDACTED]			X
MDUK42 [REDACTED]			X
MDUK43 [REDACTED]		X	X

Protocol Title	Section A	Section B	Section C
MDUK44			X
MDUK46		X	X
MDUK49		X	X
STUDY 011		X	X
MDUK12A			X
MDUK14B			X
MDUK17A			X
MDUK17C			X
MDUK28A		X	X
AUSTRIAN MC OPEN			X
MDA2			X
MDA3			X
MDA4			X
BELGIUM MC OPEN			X
BELGIUM M/C COMP		X	X
BELGIUM MC OPEN			X
FRENCH M/C COMP		X	X
MDF 1727 M/C COMP		X	X
MDF 1727 M/C COMP		X	X
MDF 1728 COMP		X	X
MDF 1729,1730,1731			X
GERMAN MC COMP		X	X
MDCH 1/2 MC OPEN			X
MDINT03 COMP		X	X
MDINT02 OPEN			X
HP/82/47A		X	X
HP/82/64A		X	X
HP/82/65A			X
HP/83/67		X	X
HP/81/74		X	X
HP/81/85A		X	X
HP/81/126A			X
HP/82/134		X	X
HP/81/148		X	X
HP/81/162A		X	X

Protocol Title	Section A	Section B	Section C
HP/81/164A [REDACTED]			X
C1101 [REDACTED] P42			X
C1102 [REDACTED] P6			X
DFG 119 [REDACTED] P30		X	X
DFG121 [REDACTED] P46			X
DFG122 [REDACTED] P47			X
DFG 123 P31		X	X
DFG 124 P32		X	X
DFG126 [REDACTED] P46			X
61201 [REDACTED] P41		X	X

Appendix B Attempted Suicide Events

Treatment	Study Title	Patent No.	Section A	Section B	Section C
	MDUK09 [REDACTED]	1 09 021			
	MDUK46 [REDACTED]	1 46 010			
	DFG 119 [REDACTED] P30	7119 011			
	DFG 119 [REDACTED] P30	7119 071			
	DFG 119 [REDACTED] P30	7119 118			
ACTIVE	STUDY 003	03.006.088			
ACTIVE	MDUK13 [REDACTED]	1 13 100		X	
ACTIVE	MDUK13 [REDACTED]	1 13 120		X	
ACTIVE	MDUK22 [REDACTED]	1 22 001		X	
ACTIVE	MDUK25 [REDACTED]	1 25 005		X	
ACTIVE	MDUK25 [REDACTED]	1 25 011		X	
ACTIVE	MDUK27 [REDACTED]	1 27 217		X	
ACTIVE	MDUK49 [REDACTED]	1 49 009		X	
ACTIVE	GERMAN MC COMP	2402 023		X	
ACTIVE	HP/82/47A [REDACTED]	6 47 002		X	
ACTIVE	DFG 119 [REDACTED] P30	7119 027		X	
ACTIVE	DFG 119 [REDACTED] P30	7119 135		X	
PAROXETINE	STUDY 002	02.004.089	X		X
PAROXETINE	STUDY 004	04.001.009			X
PAROXETINE	STUDY 004	04.002.056			X
PAROXETINE	STUDY 004	04.006.096			X
PAROXETINE	STUDY 005	05.01A.030			X
PAROXETINE	STUDY 005	05.01A.075			X
PAROXETINE	STUDY 005	05.02B.019			X
PAROXETINE	STUDY 005	05.02F.002			X
PAROXETINE	STUDY 007	07.01A.001	X	X	X
PAROXETINE	STUDY 009	09.01A.005	X		X
PAROXETINE	STUDY 009	09.01E.260	X		X
PAROXETINE	STUDY 009	09.01J.573	X		X
PAROXETINE	MDUK13 [REDACTED]	1 13 010			X
PAROXETINE	MDUK13 [REDACTED]	1 13 144		X	X
PAROXETINE	MDUK13 [REDACTED]	1 13 149		X	X
PAROXETINE	MDUK13 [REDACTED]	1 13 155		X	X
PAROXETINE	MDUK14 [REDACTED]	1 14 029			X
PAROXETINE	MDUK14 [REDACTED]	1 14 045			X
PAROXETINE	MDUK26 [REDACTED]	1 26 001		X	X

Treatment	Study Title	Patient No.	Section A	Section B	Section C
PAROXETINE	MDUK32 [REDACTED]	1 32 018		X	X
PAROXETINE	MDUK41 [REDACTED]	1 41 303			X
PAROXETINE	MDUK41 [REDACTED]	1 41 323			X
PAROXETINE	MDUK41 [REDACTED]	1 41 330			X
PAROXETINE	MDUK41 [REDACTED]	1 41 336			X
PAROXETINE	MDUK41 [REDACTED]	1 41 340			X
PAROXETINE	MDUK41 [REDACTED]	1 41 372			X
PAROXETINE	MDUK41 [REDACTED]	1 41 384			X
PAROXETINE	MDUK17A [REDACTED]	117A 004			X
PAROXETINE	MDA2 [REDACTED]	2112 004			X
PAROXETINE	BELGIUM MC OPEN	2206 021			X
PAROXETINE	BELGIUM MC OPEN	2229 014			X
PAROXETINE	FRENCH M/C COMP	2323 051		X	X
PAROXETINE	MDF 1727 M/C COMP	237G 109		X	X
PAROXETINE	MDCH 1/2 MC OPEN	2502 004			X
PAROXETINE	HP/82/47A [REDACTED]	6 47 003		X	X
PAROXETINE	HP/81/162A [REDACTED]	6162 005		X	X
PAROXETINE	C1101 [REDACTED] P42	7101 007			X
PAROXETINE	C1101 [REDACTED] P42	7101 019			X
PAROXETINE	DFG 119 [REDACTED] P30	7119 012		X	X
PAROXETINE	DFG 124 P32	7124 015		X	X
PLACEBO	STUDY 002	02.001.009	X		

Results for review of data about "suicides" in 1991 report

Prepared by:

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Biomedical Data Sciences
GlaxoSmithKline

Date: 10th May 2002

A. Placebo controlled trials

1. Identify all placebo-controlled trials used in original NDA, including paroxetine and placebo data from three-arm trials. Studies PAR-04 and PAR-014 will be excluded by virtue of their design (PAR-04 is an extension of PAR-03, and encompasses some element of crossover of treatments between the two studies; PAR-014 is described as a placebo-controlled trial in the study title, but is more accurately considered as uncontrolled). Appendix A lists all studies contributing to this analysis, while applicable suicides are identified in Appendix B.
2. Confirm denominators for the subset of patients defined by point 1.
3. Confirm list of PIDs with events that were included in the 1991 FDA submission.
4. Exclude events outside the "On-Therapy plus 30 Days Post Therapy" window. Only the on-therapy phase will be included for patients continuing into an extension phase. Events occurring during an extension phase are captured in section C analysis. (Note: on this basis events occurring during placebo run-in phases are excluded.)
5. Identify by footnote any patients excluded through point 4, that were part of the list of patients with events in the 1991 FDA submission.
6. Calculate PYE for all patients, and calculate rate of patients with event relative to exposure. Exposure is calculated only for the period on-therapy, i.e. the 30-day post-therapy window is not used in calculating exposure.
7. The hypothesis of no association between treatment and incidence of "suicide" will be tested using Fisher's exact test (two-tailed). Statistical significance will be assessed at the 5% level.
8. The number of suicide patients relative to PYE (incidence density) will be analysed using SAS[®] PROC GENMOD.
9. Refer back to original Oracle tables, e.g. paroxetine_uspat.st@usarc7.
10. Provide a cell index listing patients with the event in both treatment groups.

	Paroxetine	Placebo	P-value
n/N (%)	0/921 (0.0%)	0/554 (0.0%)	#
PYE	108	51	
n/PYE (rate relative to exposure)	0.00	0.00	#

† in both cases above, n refers to the number of patients with the event

p-values are not obtainable from analysis of zero frequencies

Two patients (7119 009 and 7119 062) have been excluded from this analysis because their suicides occurred pre-treatment.

B. Active control trials

1. Identify all active-controlled trials used in original NDA, including paroxetine and active control data from three-arm trials. Study PAR-04 will be excluded by virtue of its design (PAR-04 is an extension of PAR-03, and encompasses some element of crossover of treatments between the two studies). Appendix A lists all studies contributing to this analysis, while applicable suicides are identified in Appendix B.
2. Confirm denominators for the subset of patients defined by point 1.
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4. Exclude events outside the "On-Therapy plus 30 Days Post Therapy" window. Only the on-therapy phase will be included for patients continuing into an extension phase. Events occurring during an extension phase are captured in section C analysis. (Note: on this basis events occurring during placebo run-in phases are excluded.)
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8. The number of suicide patients relative to PYE (incidence density) will be analysed using SAS PROC GENMOD.
9. Refer back to original Oracle tables, e.g. paroxetine_uspat.st@usarc7.
10. Provide a cell index listing patients with the event in both treatment groups.

	Paroxetine	Active Control	P-value
n/N (%)	3/1096 (0.3%)	2/1063 (0.2%)	>0.999
PYE	136	120	
n/PYE (rate relative to exposure)	0.022	0.017	0.7588

† in both cases above, n refers to the number of patients with the event

An active control patient (2371 054) has been excluded from the count of events in this table because the event occurred 31 days post treatment.

An active control patient (6 67 002) who had a missing onset date for the adverse event "Suicide" has been included in the above analysis.

A paroxetine patient (1 13 126) has been excluded from the count of events in this table because the event occurred during the open label part of the study.

Two patients (7119 009 and 7119 062) have been excluded from this analysis because their suicides occurred pre-treatment.

C. All Paroxetine Data

1. Include data from all studies, both controlled and uncontrolled, including extension phases. Appendix A lists all studies contributing to this analysis, while applicable suicides are identified in Appendix B.
2. Confirm denominators for the subset of patients defined by point 1.
3. Confirm list of PIDs with events that were included in the 1991 FDA submission.
4. Exclude events outside the "On-Therapy plus 30 Days Post Therapy" window. (Note: on this basis events occurring during placebo run-in phases are excluded.)
5. Identify by footnote any patients excluded through point 4, if any, that were part of the list of patients with events in the 1991 FDA submission.
6. Calculate PYE for all patients, and calculate rate of patients with event relative to exposure. Exposure is calculated only for the period on-therapy, i.e. the 30-day post-therapy window is not used in calculating exposure.
7. Refer back to original Oracle tables, e.g. paroxetine_uspat.st@usarc7.
8. Provide a cell index listing patients with the event in both treatment groups.

	Paroxetine
n/N (%)	5/2963 (0.2%)
PYE	1008
n/PYE (rate relative to exposure)	0.005

† in both cases above, n refers to the number of patients with the event

Appendix A Study Population

Protocol Title	Section A	Section B	Section C
STUDY 001	X		X
STUDY 002	X		X
STUDY 003	X	X	X
STUDY 004			X
STUDY 005			X
STUDY 006		X	X
STUDY 007	X	X	X
STUDY 009	X		X
MDUK04 [REDACTED]		X	X
MDUK05 [REDACTED]			X
MDUK06 [REDACTED]	X		X
MDUK07 [REDACTED]	X	X	X
MDUK09 [REDACTED]	X		X
MDUK12 [REDACTED]	X	X	X
MDUK13 [REDACTED]		X	X
MDUK14 [REDACTED]			X
MDUK20 [REDACTED]		X	X
MDUK22 [REDACTED]		X	X
MDUK24 [REDACTED]			X
MDUK25 [REDACTED]		X	X
MDUK26 [REDACTED]		X	X
MDUK27 [REDACTED]		X	X
MDUK28 [REDACTED]		X	X
MDUK29 [REDACTED]		X	X
MDUK30 [REDACTED]		X	X
MDUK32 [REDACTED]		X	X
MDUK34 [REDACTED]			X
MDUK35 [REDACTED]		X	X
MDUK37 [REDACTED]			X
MDUK38 [REDACTED]		X	X
MDUK40 [REDACTED]			X
MDUK41 [REDACTED]			X
MDUK42 [REDACTED]			X
MDUK43 [REDACTED]		X	X

Protocol Title	Section A	Section B	Section C
Mduk44 [REDACTED]			X
Mduk46 [REDACTED]		X	X
Mduk49 [REDACTED]		X	X
STUDY 011		X	X
Mduk12A [REDACTED]			X
Mduk14B [REDACTED]			X
Mduk17A [REDACTED]			X
Mduk17C [REDACTED]			X
Mduk28A [REDACTED]		X	X
AUSTRIAN MC OPEN			X
MDA2 [REDACTED]			X
MDA3 [REDACTED]			X
MDA4 [REDACTED]			X
BELGIUM MC OPEN			X
BELGIUM M/C COMP		X	X
BELGIUM MC OPEN			X
FRENCH M/C COMP		X	X
MDF 1727 M/C COMP		X	X
MDF 1728 COMP		X	X
MDF 1729,1730,1731			X
GERMAN MC COMP		X	X
MDCH 1/2 MC OPEN			X
MDINT03 [REDACTED] COMP		X	X
MDINT02 [REDACTED] OPEN			X
HP/82/47A [REDACTED]		X	X
HP/82/64A [REDACTED]		X	X
HP/82/65A [REDACTED]			X
HP/83/67 [REDACTED]		X	X
HP/81/74 [REDACTED]		X	X
HP/81/85A [REDACTED]		X	X
HP/81/126A [REDACTED]			X
HP/82/134 [REDACTED]		X	X
HP/81/148 [REDACTED]		X	X
HP/81/162A [REDACTED]		X	X

Protocol Title	Section A	Section B	Section C
HP/81/164A [REDACTED]			X
C1101 [REDACTED] P42			X
C1102 [REDACTED] P6			X
DFG 119 [REDACTED] P30		X	X
DFG121 [REDACTED] P46			X
DFG122 [REDACTED] P47			X
DFG 123 P31		X	X
DFG 124 P32		X	X
DFG126 [REDACTED] P46			X
61201 [REDACTED] P41		X	X

Appendix B Suicide Events

Treatment	Study Title	Patient No.	Section A	Section B	Section C
PLACEBO RUN-IN	DFG 119 [REDACTED] P30	7119 009			
PLACEBO RUN-IN	DFG 119 [REDACTED] P30	7119 062			
ACTIVE	MDF 1727 M/C COMP	237I 054			
ACTIVE	HP/83/67 [REDACTED]	6 67 002		X	
ACTIVE	DFG 124 P32	7124 023		X	
PAROXETINE	MDUK13 [REDACTED]	1 13 126			X
PAROXETINE	BELGIUM MC OPEN	2206 005			X
PAROXETINE	GERMAN MC COMP	2406 149		X	X
PAROXETINE	HP/82/47A [REDACTED]	6 47 003		X	X
PAROXETINE	DFG 124 P32	7124 012		X	X

Two placebo run-in patients (7119 009 and 7119 062) have been excluded from all analysis.

Active control patients do not contribute to section C analysis (All Paroxetine Data)

An active control patient (237I 054) has been excluded from the section B analysis because the event occurred 31 days post treatment.

A paroxetine patient (1 13 126) has been excluded from the section B analysis because the event occurred during the open label part of the study.

An active control patient (6 67 002) who had a missing onset date for the adverse event "Suicide" has been included in the section B analysis.