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

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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).

000002

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 LAVIN		X	X
MDUK05 CORELESS			X
MDUK06 NAYLOR	X		X
MDUK07 SILVERSTONE	X	X	X
MDUK09 EDWARDS	X		X
MDUK12 TRIMBLE	X	X	X
MDUK13 WADE		X	X
MDUK14 TYRER			X
MDUK20 AKHTAR		X	X
MDUK22 CARLE/PENDER		X	X
MDUK24 SHANKS			X
MDUK25 ECCLESTONE		X	X
MDUK26 DORMAN		X	X
MDUK27 PEET/GHADVI		X	X
MDUK28 BRAY		X	X
MDUK29 SUD		X	X
MDUK30 SHUR		X	X
MDUK32 BEAUMONT		X	X
MDUK34 TRIMBLE			X
MDUK35 TOONE		X	X
MDUK37 MC			X
MDUK38 CHAKRAVARTI		X	X
MDUK40 GHOSE			X
MDUK41 WADE			X
MDUK42 WADE			X
MDUK43 WINSLOW		X	X
	34	9	19 34

PAR

Protocol Title	Section A	Section B	Section C
MDUK44 RAO/SINGH			X
MDUK46 ADDALA		X	X
MDUK49 HUTCHINSON		X	X
STUDY 011		X	X
MDUK12A TRIMBLE			X
MDUK14B TYRER			X
MDUK17A CROME			X
MDUK17C CROME			X
MDUK28A BRAY		X	X
AUSTRIAN MC OPEN			X
MDA2 HEBENSTREIT			X
MDA3 HEBENSTREIT			X
MDA4 HEBENSTREIT			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 GAGIANO COMP		X	X
MDINT02 GAGIANO OPEN			X
HP/82/47A VERVARCKE		X	X
HP/82/64A GOFFAUX		X	X
HP/82/65A PRIEST			X
HP/83/67 MARGO		X	X
HP/81/74 LAXENAIRE		X	X
HP/81/85A VARACKX-HAENEN		X	X
HP/81/126A FELDMAN			X
HP/82/134 JAUHAR		X	X
HP/81/148 RICHOU		X	X
HP/81/162A BATTEGAY		X	X

Protocol File	Section A	Section B	Section C
HP/81/164A GAIND			X
C1101 BORUP P42			X
C1102 SKAUSIG P6			X
DFG 119 DUAG P30		X	X
DFG121 THOMSEN P46			X
DFG122 VANGTORP P47			X
DFG 123 P31		X	X
DFG 124 P32		X	X
DFG126 PAUSER P46			X
61201 L.LAURSEN P41		X	X

Appendix B Attempted Suicide Events

Treatment	Study Title	Patient No	Section A	Section B	Section C
	MDUK09 EDWARDS	1 09 021			
	MDUK46 ADDALA	1 46 010			
	DFG 119 DUAG P30	7119 011			
	DFG 119 DUAG P30	7119 071			
	DFG 119 DUAG P30	7119 118			
ACTIVE	STUDY 003	03.006.088			
ACTIVE	MDUK13 WADE	1 13 100		X	
ACTIVE	MDUK13 WADE	1 13 120		X	
ACTIVE	MDUK22 CARLE/PENDER	1 22 001		X	
ACTIVE	MDUK25 ECCLESTONE	1 25 005		X	
ACTIVE	MDUK25 ECCLESTONE	1 25 011		X	
ACTIVE	MDUK27 PEET/GHADVI	1 27 217		X	
ACTIVE	MDUK49 HUTCHINSON	1 49 009		X	
ACTIVE	GERMAN MC COMP	2402 023		X	
ACTIVE	HP/82/47A VERVARCKE	6 47 002		X	
ACTIVE	DFG 119 DUAG P30	7119 027		X	
ACTIVE	DFG 119 DUAG 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 WADE	1 13 010			X
PAROXETINE	MDUK13 WADE	1 13 144		X	X
PAROXETINE	MDUK13 WADE	1 13 149		X	X
PAROXETINE	MDUK13 WADE	1 13 155		X	X
PAROXETINE	MDUK14 TYRER	1 14 029			X
PAROXETINE	MDUK14 TYRER	1 14 045			X
PAROXETINE	MDUK26 DORMAN	1 26 001		X	X

Treatment	Study Title	Patient No.	Section A	Section B	Section C
PAROXETINE	MDUK32 BEAUMONT	1 32 018		X	X
PAROXETINE	MDUK41 WADE	1 41 303			X
PAROXETINE	MDUK41 WADE	1 41 323			X
PAROXETINE	MDUK41 WADE	1 41 330			X
PAROXETINE	MDUK41 WADE	1 41 336			X
PAROXETINE	MDUK41 WADE	1 41 340			X
PAROXETINE	MDUK41 WADE	1 41 372			X
PAROXETINE	MDUK41 WADE	1 41 384			X
PAROXETINE	MDUK17A CROME	117A 004			X
PAROXETINE	MDA2 HEBENSTREIT	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 VERVARCKE	6 47 003		X	X
PAROXETINE	HP/81/162A BATTEGAY	6162 005		X	X
PAROXETINE	C1101 BORUP P42	7101 007			X
PAROXETINE	C1101 BORUP P42	7101 019			X
PAROXETINE	DFG 119 DUAG P30	7119 012		X	X
PAROXETINE	DFG 124 P32	7124 015		X	X
PLACEBO	STUDY 002	02.001.009	X		

May 2, 2002

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Division of Neuropharmacological Drug Products
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HFD-120, WOC2, Room 4049
1451 Rockville Pike
Rockville, MD 20852

Re: NDA 20-031; PAXIL® (paroxetine hydrochloride) Tablets
General Correspondence: Clinical, Statistical

Dear Dr. Katz:

Reference is made to our approved New Drug Applications for Paxil® (paroxetine hydrochloride) Tablets, Oral Suspension, and Controlled-Released Tablets, i.e. NDA 20-031, NDA 20-710 and NDA 20-936, respectively.

Submitted herein is an additional analysis of results from a review of data regarding "suicide attempts" originally submitted May 10, 1991 to NDA 20-031. The enclosed attachments describe the methodology and summary results obtained from (i) analysis of attempts in placebo controlled studies, patients randomized to Paxil vs. those randomized to placebo, (ii) analysis of attempts in active controlled studies, patients randomized to Paxil vs. those randomized to active control and (iii) qualitative data from all studies, both controlled and uncontrolled, including extension phases. Identification of the specific protocols utilized in these analyses, and a cell index of individual patient ID numbers are provided as Appendix A and B, respectively.

Please do not hesitate to contact me at (610) 917-5970 should you have any questions or require additional information.

Sincerely,

Thomas F. Kline
Director
Regulatory Affairs

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