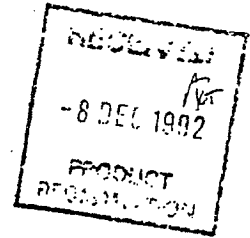




Central Research
Sandwich, Kent

Memorandum

Date: 7th December 1992
To: Dr H Krish, Germany
cc: Dr R Alvar, France
Dr M Guttauria, New York
Dr A J Grace Dr P Hodges
Ms V M Marshall Dr J A Milson
Mr D J Shannon Dr R H Swift
From: Dr S J Felstead
Subject: Sertraline Study STL-CR-90-002



In reply to your phone call, I attach the following analyses of the sertraline, clomipramine, placebo in-patient study.

- 1) Overall HAM-D analysis
- 2) HAM-D item 1 analysis
- 3) HAM-D item 3 analysis

The total analysis comprises over 70 patients per group, therefore the study achieves its required power reported to BGA (Table 1).

These analyses have been undertaken both by hand from listing and direct from the provided SAS datasets. They have been reviewed and checked by 2 statisticians and a physician. They include all data currently available, over seventy patients per group. The analyses are all intent-to-treat rather than evaluable, because very few patients would be excluded (i.e. nearly all received the minimum of 11 days therapy).

The findings from the analyses of the entire available database, is that clomipramine is significantly superior to both sertraline and placebo, and that sertraline shows no trend to be better than placebo. This is true for total HAM-D score (Table 2), HAM-D-1 score (specific for depression (Table 3)) and for HAM-D-3 (suicidal ideation (Table 4)). In fact the latter shows a trend for placebo to be better than sertraline. Randomisation and drug supplies have been checked and appear to accord. Further analyses have been conducted and appear to show a centre/time effect.

In brief the study started as a 70 patient/group study (=210) and 24 centres were activated. The study was then extended at the behest of Central Research to 300 patients. Therefore a further 12 then 8 centres (total=20) were added to allow an increase in both rate of and total recruitment (Table 5). The first 24 centres data (c150/220 patients available) showing sertraline to be worse than placebo and clomipramine better than placebo (Table 6). The next 20 centres

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(c70/220 patients), show sertraline to be equivalent to clomipramine, both better than placebo (Table 7). Therefore there is a centre or time effect seen with sertraline. I should note that the placebo and clomipramine responses in the first 24 centres and the last 20 centres are near identical, so the effect is confined to sertraline alone.

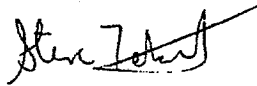
We predict that if this trend is repeated through to the full 300 patient study that sertraline should at least show a trend to be better than placebo, although it will not achieve statistical significance.

At present however 75% of the available data is from the first 24 centres therefore there is no way of distinguishing sertraline from placebo.

The Central Research regulatory assessment is that these data are not currently helpful in achieving registration and that further time to complete the study and investigate centre effects (assuming they are maintained) is necessary.

I hope this clarifies the data so far.

Best Regards,



Dr S J Felstead

SJF:kw/CDB

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SUMMARY OF PATIENTS INCLUDED IN ITT ANALYSIS

| | Treatment Group | | | Total |
|--------------------------|-----------------|--------------|---------|-------|
| | SERTRALINE | CLOMIPRAMINE | PLACEBO | |
| Number of Patients | 74 | 78 | 71 | 223 |
| Included in ITT Analysis | 71 | 76 | 71 | 218 |

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TABLE 3/1A ²

SUMMARY TABLE FOR BASELINE TO ENDPOINT CHANGE OF HAND 17 ITEMS

| Analysis of Variance | | | | |
|----------------------|-----|-------------|------|--------|
| Source | df | Mean Square | F | P |
| Treatment | 2 | 625.8 | 7.44 | 0.0008 |
| Residual | 215 | 84.2 | | |

| | | |
|--------------|---------------|--------|
| Sertraline | Adjusted Mean | -9.51 |
| | Std. Dev. | 9.59 |
| Clomipramine | Adjusted Mean | -14.87 |
| | Std. Dev. | 9.26 |
| Placebo | Adjusted Mean | -10.25 |
| | Std. Dev. | 8.65 |

CONTRAST

| Comparison | Difference Between Adjusted Means | 95% Confidence Limits on Difference Between Means | |
|-------------------------|-----------------------------------|---|-------|
| | | Lower | Upper |
| Treatment Comparison | | | |
| Sertraline-Clomipramine | 5.36 | 2.38, | 8.34 |
| Sertraline-Placebo | 0.75 | -2.29, | 3.78 |
| Clomipramine-Placebo | -4.61 | -7.60, | -1.63 |

Run date=04DEC92

P < 0.05
P > 0.05
P < 0.05

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TABLE 3.2A

SUMMARY TABLE FOR BASELINE TO ENDPOINT CHANGE OF HAMD ITEM 1

| Analysis of Variance | | | | |
|----------------------|-----|-------------|------|--------|
| Source | df | Mean Square | F | P |
| Treatment | 2 | 8.0 | 5.27 | 0.0058 |
| Residual | 215 | 1.5 | | |

| | | |
|--------------|---------------|-------|
| Serttraline | Adjusted Mean | -1.37 |
| | Std. Dev. | 1.24 |
| | N | 71 |
| Clomipramine | Adjusted Mean | -1.93 |
| | Std. Dev. | 1.16 |
| | N | 76 |
| Placebo | Adjusted Mean | -1.37 |
| | Std. Dev. | 1.29 |
| | N | 71 |

| CONTRAST | | | |
|--------------------------|-----------------------------------|---|-------|
| Comparison | Difference Between Adjusted Means | 95% Confidence Limits on Difference Between Means | |
| | | Lower | Upper |
| Treatment Comparison | | | |
| Serttraline-Clomipramine | 0.57 | 0.17, | 0.97 |
| Serttraline-Placebo | 0.00 | -0.41, | 0.41 |
| Clomipramine-Placebo | -0.57 | -0.97, | -0.17 |

Run date=04DEC92

$P < 0.05$
 $P > 0.05$
 $P < 0.05$

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TABLE 3 ~~3A~~ 4
SUMMARY TABLE FOR BASELINE TO ENDPOINT CHANGE OF HAND ITEM 3

| Analysis of Variance | | | | |
|----------------------|-----|-------------|------|--------|
| Source | df | Mean Square | F | P |
| Treatment | 2 | 4.5 | 3.25 | 0.0405 |
| Residual | 215 | 1.4 | | |

| | | |
|--------------|---------------|-------|
| Serttraline | Adjusted Mean | -0.51 |
| | Std. Dev. | 1.26 |
| | N | 71 |
| Clomipramine | Adjusted Mean | -1.00 |
| | Std. Dev. | 1.05 |
| | N | 76 |
| Placebo | Adjusted Mean | -0.76 |
| | Std. Dev. | 1.20 |
| | N | 71 |

| CONTRAST | | | | |
|--------------------------|-----------------------------------|---|-------|--|
| Comparison | Difference Between Adjusted Means | 95% Confidence Limits on Difference Between Means | | |
| | | Lower | Upper | |
| Treatment Comparison | | | | |
| Serttraline-Clomipramine | 0.49 | 0.11, | 0.87 | |
| Serttraline-Placebo | 0.25 | -0.13, | 0.64 | |
| Clomipramine-Placebo | -0.24 | -0.62, | 0.14 | |

Run date=04DEC92

P < 0.05
P > 0.05
P > 0.05

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SUMMARY OF PATIENTS INCLUDED IN ITT ANALYSIS
BY CENTRE GROUPING 1 VS 2+3

| Centre Grouping | Treatment Group | | | Total |
|----------------------------|--------------------------|--------------|---------|-------|
| | SERTRALINE | CLOMIPRAMINE | PLACEBO | |
| 1 24 <i>Cohort</i> | Number of Patients | 51 | 53 | 104 |
| | Included in ITT Analysis | 49 | 51 | 100 |
| 2 12+8 <i>Cohort</i> | Number of Patients | 23 | 25 | 48 |
| | Included in ITT Analysis | 22 | 25 | 47 |
| TOTAL | Number of Patients | 74 | 78 | 152 |
| | Included in ITT Analysis | 71 | 76 | 147 |

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TABLE 31E

SUMMARY TABLE FOR BASELINE TO ENDPOINT CHANGE OF HAND 17 ITEMS
Centre 1 only = 24 cases (early responders)

| Analysis of Variance | | | | |
|----------------------|-----|-------------|------|--------|
| Source | df | Mean Square | F | P |
| Treatment | 2 | 690.4 | 7.98 | 0.0005 |
| Residual | 146 | 86.5 | | |

| | | |
|--------------|---------------|--------|
| Serttraline | Adjusted Mean | -7.35 |
| | Std. Dev. | 9.69 |
| | N | 49 |
| Clomipramine | Adjusted Mean | -14.75 |
| | Std. Dev. | 9.31 |
| | N | 51 |
| Placebo | Adjusted Mean | -10.49 |
| | Std. Dev. | 8.88 |
| | N | 49 |

CONTRAST

| Comparison | Difference Between Adjusted Means | 95% Confidence Limits on Difference Between Means | |
|--------------------------|-----------------------------------|---|-------|
| | | Lower | Upper |
| Treatment Comparison | | | |
| Serttraline-Clomipramine | 7.40 | 3.71, | 11.08 |
| Serttraline-Placebo | 3.14 | -0.58, | 6.86 |
| Clomipramine-Placebo | -4.26 | -7.94, | -0.57 |

Run date=04DEC92

120.05
P > 0.05
P < 0.05

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TABLE 34E 7

SUMMARY TABLE FOR BASELINE TO ENDPOINT CHANGE OF HAND 17 ITEMS
Centres 2+3 only = 20 cases (15a renumbers)

Analysis of Variance

| Source | df | Mean Square | F | P |
|-----------|----|-------------|------|--------|
| Treatment | 2 | 192.4 | 2.69 | 0.0751 |
| Residual | 66 | 71.4 | | |

| | | |
|--------------|---------------|--------|
| Serttraline | Adjusted Mean | -14.32 |
| | Std. Dev. | 7.54 |
| | N | 22 |
| Clomipramine | Adjusted Mean | -15.12 |
| | Std. Dev. | 9.32 |
| | N | 25 |
| Placebo | Adjusted Mean | -9.73 |
| | Std. Dev. | 8.27 |
| | N | 22 |

CONTRAST

| Comparison | Difference Between Adjusted Means | 95% Confidence Limits on Difference Between Means | |
|--------------------------|-----------------------------------|---|-------|
| | | Lower | Upper |
| Treatment Comparison | | | |
| Serttraline-Clomipramine | 0.80 | -4.11, | 5.72 |
| Serttraline-Placebo | -4.59 | -9.66, | 0.48 |
| Clomipramine-Placebo | -5.39 | -10.31, | -0.48 |

Run date=04DEC92

$P > 0.05$
 $P > 0.05$
 $P < 0.05$

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