

Revised by MCC as per
Depote p277.

DRAFT MINUTES: 4/22/97 TELECONFERENCE

Paroxetine Study 329 Efficacy Analyses

Participants

Investigators: Drs. Carlson, Clarke, Emslie, Klein, Kusumakar, Kutcher, Papatheodorou, Ryan, Strober, Wagner, Weller (Please let us know if we missed anyone.)

SmithKline Beecham: Drs. and Messrs. Bushnell, Gergel, McCafferty, Wheeler

Topics

- 1. Whether to break the blind at end of the acute phase?

We agreed to break the blind at the end of the acute phase and to analyze the acute phase data while the continuation phase winds down. To avoid bias, individual patient data listings and the randomization codes will not be provided to the investigators until the end of the continuation phase.

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- 2. Definition of "response" during the acute phase

There will be two definitions:

a. "Remission": HAM-D score ≤ 8

b. "Responder": HAM-D score ≤ 8 or reduction from baseline in HAM-D score $\geq 50\%$ (current definition in protocol)

1st APPROXIMATE OF
PROTECTIVE ORDER
+? OF
REMISSION

Note: Hopefully, either definition of response according to HAM-D would be supported by a CGI Improvement score of 1 or 2.

- 3. Definition of "relapse" during the continuation phase

Operationally and according to the protocol, patients who were "responders" at the end of the acute phase were allowed to enter the continuation phase.

However, "relapse" during the continuation phase will be evaluated only for patients who were in full remission (HAM-D score ≤ 8) at the end of the acute phase and entry into the continuation phase.

So denominator is larger than numerator can ever be.

ie Finding relapse data

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4. **Subsidiary analyses of response by patient covariates and definition of subgroups**

- more were implemented - ? because they didn't fall precisely*
- a. Presence of atypical depression. **Dr. Klein has provided the following definition (please see attached FAX):**
- 1). Mood reactivity (item 14 of K-SADS-L on CRF page 43 with intensity score between 0 and 3 and occurring $\geq 50\%$ of "usual % of normal")
 - plus** 2) One or more: lack of energy; rejection sensitivity; hypersomnia; and either increased appetite or weight gain
 - Lack of energy (item 40 of K-SADS-L on CRF page 45 with intensity score between 4 and 6)
 - Rejection sensitivity (item 72 of K-SADS-L on CRF page 48 with intensity score of 5 or 6, or item 74 with intensity score between 4 and 6)
 - Hypersomnia (item 83 of K-SADS-L on CRF page 48 with intensity score between 4 and 6)
 - Increased appetite (item 103 of K-SADS-L on CRF page 50 with intensity score between 4 and 6) **or** weight gain (item 106 of K-SADS-L on CRF page 50 with gain ≥ 10 lbs)
 - plus** 3) Lack of qualification for melancholic subtype of depression
- b. Presence of melancholic/endogenous subtype of depression (*Dr. Ryan: please provide SB with criteria for definition from K-SADS*)
- c. Current (i.e., "continuing" or "both" on K-SADS-L) anxiety disorder (combine separation anxiety disorder, panic disorder \pm agoraphobia, agoraphobia, social phobia, and generalized anxiety disorder)
- d. Current (i.e., "continuing" or "both" on K-SADS-L) for any comorbid disorder other than major depressive episode
- e. Age at first onset of depression (**Location of this field in the database should correspond to item 119 of K-SADS-L on CRF page 52**)
- f. Number of episodes of major depressive disorder (**Location of this field in database should correspond to item 118 of K-SADS-L on CRF page 52**)

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- g. Family history of major depressive disorder (*Investigators: Whether there was a family history of MDD was never queried directly as a "yes" or "no" answer to a question in the case report form. Should we use a "yes" answer to question 8 on the Family History- Epidemiologic form to identify those patients who had a family history of MDD? Or do you suggest an alternative method?*)
- h. Thyroid function indices (TSH, T₃, T₄, and T₃/T₄ ratio) prior to treatment

5. **Relationship of patient's age to frequency of side effects**

As a subsidiary safety analysis, SB agreed to tabulate the frequency of treatment-emergent side effects in two age subgroups younger adolescents (12 to 14 y. o. inclusive) and older adolescents. (This subgroup analysis is to be conducted using the adverse event tables.)

6. **Computation of K-SADS affect subscale scores**

An issue was raised regarding computation of scores on the 9-item affect subscale on the K-SADS if an item is missing. The K-SADS scores will be adjusted for any missing items using the same algorithm for missing items on the HAM-D scale (section 3.13.3 of skeleton report).

7. **Survival analysis**

In a previous teleconference, we agreed to examine the time to sustained response (i.e., response lasting until endpoint) during the acute phase and the time to relapse during the continuation phase in each treatment group using a survival-type analysis such as the Kaplan-Meier analysis.

8. **Analyses of results from Sickness Impact Profile (SIP), Self-Perception Profile (SPP), and Autonomous Functioning Checklist (AFC)**

Several investigators expressed interest in whether these instruments might show a change in the patients' functioning after treatment. These scales were completed at baseline and at the end of the acute phase.

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Dr. Kutcher discussed these instruments with Jim McCafferty, Rosemary Oakes, Norma Pugh, and Sarah Wheeler via teleconference on 5/6/97.

Possible relationships will be investigated between total scores and subscores on these three scales with the HAM-D total scores, the K-SADS affect subscale scores, and the response ("yes" or "no") at the endpoint of the acute phase.

Self-Perception Profile

Of interest is whether an improvement in depressive symptomatology is associated in a change in the patient's sense of self-esteem.

The issue of whether the patients understood the format and completed it appropriately was discussed. A 1995 publication criticized the original format (used in this study) and suggested a simplified, more "user-friendly" version. We decided that the data will be analyzed if a high proportion of the patients completed the scale according to the directions.

If the data are useable, then each question will be coded on a 0 (most negative rating of self-esteem) to 3 (most positive rating of self-esteem), and a total score calculated. If the coding template can be located, subscores may also be calculated.

***Ms. Oakes, Ms. Pugh:* Assess what proportion of patient checked two answers (one on each side) for many questions or checked answers consistently on one side of the page only.**

***Dr. Kutcher:* Please confirm the list of the questions for which higher self-esteem is indicated by a response on the right-side question versus the left-side question and provide the scoring template, if available.**

Autonomous Functioning Checklist

Of interest is whether improvement in depressive symptomatology is associated with an improvement in social functioning. If so, is there a different response in patients receiving placebo compared with patients receiving active study medication?

*Should strongly monitoring in
these measures at end
of data collection*

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Questions 1-58 are coded as 0 to 4 and questions 59-78 as 1 (yes) or 0 (no). A total score and subscores for self and family care (Q 1-22), management (Q 23-42), recreational activity (Q 43-58) and social and vocational activities (Q 59-78) will be calculated. Higher scores indicate more autonomous functioning. Normative data may be available from Dr. Carl Feinstein at the Kennedy-Krieger Institute in Baltimore but are probably unpublished.

Mr. McCafferty: Contact Dr. Feinstein to ask for background information on this scale and any available normative information.

Sickness Impact Profile

Of interest is whether patients whose depressive symptoms have responded to treatment consider that their functioning in daily living has also improved.

In the version of the scale we used for these adolescents, the first 2 questions rate "present health" and "present quality of life" on an ordinal scale from 1 (very good) to 5 (very poor). There follow 6 subgroups comprised of 6 to 17 questions, each coded as 1 (yes) or 0 (no). The subgroups are: sleep/rest; home management; social interaction; alertness behavior; communication; and recreation and pastimes.