August 6, 1968

Dr. Gaston-Germain Trigos
Wyeth Laboratories
Box 8299
Philadelphia, Pennsylvania 19101

Dear Dr. Trigos:

It was a pleasure to discuss studies of WY 3263 and WY 4036. We have had the opportunity to review the data submitted and believe we can contribute to your study program.

WY 4036. These initial reports of this novel compound report anti-anxiety and anti-convulsant properties. Most unusual is the report of amnesic properties in patients.

I reviewed the available EEG data, seeking a better definition of its neurophysiology. Motor activity in mice was suppressed, with WY 4036 being 100-200 x as effective as chlordiazepoxide. The EEG activity in cats showed a "decreased frequency and further spindling" at intravenous doses of 1 mg/kg to 4 mg/kg. It is reported an exceptional anticonvulsant, particularly against metrazole.

The clinical data reports ataxia and sedation during administration of 5-10 mg/day oral, and nervousness, insomnia, diarrhea or constipation two to three days after cessation of WY 4036.

Two studies are suggested in the population available in these laboratories.

1. EEG Profile. As indicated, we find the EEG profile in volunteers, supported by similar data in patients useful in classifying new psychoactive drugs, and identifying target populations. If a parenteral form of WY 4036 is available, an EEG profile study can be done rapidly, and a suggested protocol is enclosed.

If only an oral form is available, a similar study can be done but it requires more extensive material and a longer period of study. The protocol indicates the differences in design in the supplement.

2. Clinical trial. The anti-anxiety activity of WY 4036 should properly be tested in a wide variety of anxiety subjects. Our ongoing studies of anti-anxiety agents in a mental health clinic population permit the introduction of WY 4036 in either an open study or a random comparison with chlordiazepoxide (our present standard).

I would also suggest that a study of the sedative effects of WY 4036, especially its effects on the sleep - EEG ("sleep-prints") be considered. The data cannot be collected in my laboratories, but we are uniquely equipped to analyze data recorded carefully elsewhere. The data can be collected in collaborating laboratories, and if this is of interest, I will be glad to provide the details.

WY 3263. The extensive trials already completed are clear and the new efforts that may be necessary for a better delineation of clinical applications may come best from the extensive clinical trials when ~~the~~ iprindole is released. The data does not include reports of EEG examinations. These would be useful to define the neurophysiologic basis of the clinical response. In the face of the extensive clinical data, perhaps such data would only satisfy our scientific fancy.

An EEG profile study may yet be useful in completing the submission, and if so, can be assessed in a fashion similar to that suggested in the protocol for WY 4036.

Two protocols are enclosed, for an EEG profile analysis and a clinical trial of WY 4036. Protocols for a sleep-print EEG study of WY 4036 and an EEG profile of WY 3263 will be provided.

Thank you for the opportunity of reading this interesting material.

Sincerely yours,

Max Fink, M.D.
Professor of Psychiatry

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