SYNOPSIS

TITLE FLUVOXAMINE IN THE TREATMENT OF OBSESSIVE COMPULSIVE DISORDER: A MULTICENTER DOUBLE-BLIND PLACEBO-CONTROLLED STUDY IN OUTPATIENT CHILDREN AND ADOLESCENTS

INVESTIGATORS Twenty investigative centers (22 investigators) participated in the study.

OBJECTIVE(s) The primary objective of this study was to compare the relative safety and efficacy of 50-200 mg/day of fluvoxamine given for up to 10 weeks to that of placebo in the treatment of outpatient children and adolescents (ages 8 to 17 years old) with obsessive compulsive disorder. A secondary objective was to assess the safety and efficacy of fluvoxamine treatment for up to 1 year in this population (open-label Extension phase).

STUDY DESIGN This was a 10-week, randomized, double-blind, placebo-controlled multi-center study of the safety and efficacy of fluvoxamine in two parallel groups, each consisting of 50-60 outpatient children and adolescents with obsessive compulsive disorder, for a total of 120 patients. Twenty centers participated in this study. Centers were allowed to enroll an unspecified number of patients who met entrance criteria, with pre-approval from the Solvay Project Director.

In addition to the double-blind Core phase of the study, a one year open-label Extension phase was available for those patients who either prematurely terminated from Core due to lack of efficacy after six weeks of treatment or who completed the 10-week study. An additional year of
Humanitarian treatment with fluvoxamine was offered to those patients who completed the one year open-label Extension phase.

PATIENT SELECTION CRITERIA. Outpatients, 8 through 17 years of age and of either sex, with a DSM-III-R diagnosis of Obsessive Compulsive Disorder (300.30), that had been present for at least 6 months, were permitted in the study.

TREATMENT SUMMARY. Patients received 10 weeks treatment with either fluvoxamine or placebo. One hundred twenty patients were randomized into the Core phase, 57 to fluvoxamine treatment and 63 to placebo treatment. The average age was 13.4 years in the fluvoxamine group and 12.7 years in the placebo group. Forty-six patients, 19 in the fluvoxamine group and 27 in the placebo group, withdrew from the study before completing 10 weeks of treatment. Three patients in the fluvoxamine group and one in the placebo group withdrew for reasons related to adverse events.

STUDY STATUS. The Core phase of the study is completed. The Extension phase is ongoing with less than 10 active patients. The Humanitarian phase was terminated as of 02/28/95 since fluvoxamine is now available in the United States.

PATIENT CHARACTERISTICS. In total, 134 patients were screened for the study, i.e., they signed an informed consent and were given placebo for the washout/screening phase. Fourteen patients were discontinued during or at the end of the baseline period as screen failures. One hundred twenty patients were randomized, 57 to fluvoxamine and 63 to placebo treatment.
The patients ranged in age from 8.50 to 17.90 years, approximately half were female (47%) and the majority of the patients (96%) were white. Demographic characteristics were comparable between both treatment groups.

**RESULTS: EFFICACY** Efficacy was measured by the Children's Yale-Brown Obsessive Compulsive Scale (CYBOCS), NIMH Global Obsessive Compulsive Scale (NIMH-OC), and Clinical Global Impression (CGI) at screening, baseline, interim (Day 7, 14, 21, 28, 42, and 56) visits, and Day 70 (or upon premature termination). At screening and baseline, only the "Severity of Illness" item was completed on the CGI. In addition, the NIMH Global Scale was completed at screening and baseline visits. The Children's Depression Rating Scale (CDRS-R) was collected at screening, baseline, and final visits. The Patient and Parent Global Assessments (PGI) were completed at each interim visit and at the final visit.

The efficacy results show that fluvoxamine is a more effective treatment than placebo.

**C-YBOCS-Carry Forward Analysis**

The primary efficacy variable, C-YBOCS, showed significant differences from placebo (p≤0.05) for the carry-forward analysis at Weeks 1-6, and at Week 10 with a trend toward significance (p≤0.10) at Week 8.

**C-YBOCS-Visit-Wise Analysis**

The C-YBOCS visit-wise analysis showed significant differences from placebo at Weeks 1-6 also. However, the differential dropout rate (19 placebo and 10 fluvoxamine patients) after Week 6 to enter the open-
label Extension phase early resulted in a loss of statistical significance in the visit-wise analysis after Week 6.

**Secondary Efficacy Measures**
The C-YBOCS results (primary efficacy variable) are supported by the secondary efficacy variables (i.e. NIMH-OC, CGI) in that statistically significant differences between fluvoxamine and placebo were observed from Weeks 1-10 in the carry-forward analysis and from Weeks 1-6 in the visit-wise analysis.

**RESULTS: SAFETY** Safety assessments, mainly adverse event reporting, vital signs, and laboratory results, did not identify any safety concerns associated with the use of fluvoxamine in this patient sample. Adverse events were reported by equal numbers of fluvoxamine and placebo patients. The most frequently reported adverse events (placebo-adjusted) in the fluvoxamine group were insomnia, asthenia, agitation, hyperkinesia, somnolence and dyspepsia. Only four patients (1 placebo and 3 fluvoxamine) prematurely terminated due to adverse events and none of these events were considered serious.

**CONCLUSIONS** The results of this study show that fluvoxamine treatment is statistically significantly better than placebo for the treatment of obsessive compulsive disorder in children and adolescents. Also, based on the number of patients who withdrew for adverse events, the doses of fluvoxamine employed in this study (50-200 mg/day) were well tolerated.