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<b>Proprietary Drug Name:</b> Marinol	<b>Generic Drug Name:</b> Dronabinol	<b>Condition:</b> Chemotherapy Induced Nausea and Vomiting
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**Name of Sponsor/Company:**

Solvay Pharmaceuticals

**Title of Study:**

A Double-blind, Randomized, Placebo-controlled, Parallel-group Efficacy Study of Oral Dronabinol Alone and in Combination with Ondansetron versus Ondansetron Alone in Subjects with Delayed Chemotherapy-induced Nausea and Vomiting  
Protocol No.: S175.3.102

**Investigator(s):**

37 sites had investigational product released; 17 Investigators enrolled subjects.

**Study Center(s):**

40 sites were to have participated; 18 sites screened at least one subject and 17 sites randomized at least one subject.

**Publication (Reference):**

Not Applicable

**Study Period:**

19 FEB 2003 (First Subject First Visit) –  
20 JUL 2004 (Last Subject Last Visit)

**Phase of Development:**

Phase III (Terminated early)

**Objectives:**

The primary objective was to determine the efficacy of oral dronabinol versus standard ondansetron antiemetic therapy in preventing delayed-onset chemotherapy-induced nausea and vomiting (CINV) or retching by measuring the incidence of total response of nausea and vomiting and/or retching following administration of moderate-to-high emetogenic chemotherapeutic agents.

**Methodology:**

This was a double-blind, randomized, placebo-controlled, parallel-group multicenter study of the efficacy and safety of oral dronabinol, with ondansetron as a comparator agent. Subjects were assigned to one of four treatment groups.

On Day 1 (day of chemotherapy), all subjects received standard antiemetic therapy of dexamethasone 20 mg oral (PO) plus ondansetron 16 mg intravenously (IV) prior to chemotherapy. Subjects in Group D (dronabinol), Group O (ondansetron) and Group DO (dronabinol and ondansetron) also received dronabinol 2.5 mg on Day 1 before chemotherapy and in the evening of Day 1. Subjects in Group P (placebo) received placebo for both doses on Day 1.

On Day 2 (fixed dosing), all subjects took four capsules four times a day. Subjects in Group D received dronabinol 2.5 mg four times a day (QID) (10 mg/day), subjects in Group O received ondansetron 8 mg twice a day (BID) (16 mg/day). Subjects in Group O were dosed every six hours to preserve the blind; placebo was given as the middle two doses. Subjects in Group DO received dronabinol 2.5 mg QID (10 mg/day) plus ondansetron 8 mg BID (16 mg/day), subjects in Group P received placebo four times a day.

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For Day 3 through Day 5 (flexible dosing), subjects took capsules BID or QID based on tolerance. Subjects in Group D received dronabinol 2.5 mg to 5 mg QID (10 mg to 20 mg/day), subjects in Group O received ondansetron 4 mg to 8 mg BID (8 mg to 16 mg/day), subjects in Group DO received the combination of dronabinol 2.5 to 5 mg QID (10 mg to 20 mg/day) plus ondansetron 4 mg to 8 mg BID (8 mg to 16 mg/day) and subjects in Group P received placebo QID.

In the event study medication was not tolerated, the dose could be cut in half after Day 2. Open-label rescue medications to treat intolerable nausea and/or vomiting were available. Subjects requiring rescue medication continued in the study to Day 6, Day 7 or Day 8 of Follow-up or to Early Termination.

Clinic visits occurred at Screening, Day 1 and at the end of the study (Day 6, Day 7, or Day 8, or at Early Termination). Information on nausea and vomiting and/or retching, was reported daily by telephone using an interactive voice response system (IVRS).

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**Number of Subjects (Planned, Consented, Randomized and Analyzed):**  
464 subjects (116 in each of four treatment groups) were planned but due to slow enrollment, the Sponsor decided to close the study after only 64 subjects were randomized (Group D, 17 subjects; Group O, 16 subjects; Group DO, 17 subjects; Group P 14 subjects). The Intent-to-Treat (ITT) population for determination of efficacy consisted of 61 of the 64 randomized subjects.

**Diagnosis and Main Criteria for Inclusion:**  
Subjects  $\geq 18$  years, undergoing moderate-to-highly emetogenic chemotherapy.

**Test Product, Dose and Mode of Administration:**  
Oral dronabinol was supplied as 2.5 mg softgel capsule; the dose range was 2.5 mg to 5 mg QID (10 mg to 20 mg/day).

**Duration of Treatment:**  
Five days

**Reference Therapy, Dose and Mode of Administration:**  
Oral ondansetron was supplied as 4 mg tablets encapsulated in a hard gelatin capsule; the dose range was 4 mg to 8 mg BID (8 mg to 16 mg/day).  
  
Oral placebo was supplied as softgel capsules (dronabinol placebo) and hard capsules (ondansetron placebo). Placebo was administered QID.

**Criteria for Evaluation:**  
*Efficacy:*  
  
*Primary Objective:*  
The primary efficacy measure was the incidence of total response of nausea and vomiting and/or retching following administration of moderate-to-high emetogenic chemotherapeutic agents. The total response of nausea and vomiting/retching was defined as no vomiting and/or retching, an intensity of nausea of  $< 5$  mm on the visual analog scale (VAS) and no use of rescue medication.

*Secondary Objectives:*  
To evaluate the following:

1. Complete responder rate (no vomiting/retching, intensity of nausea of  $\leq 30$  mm on the VAS and no use of rescue medication)
2. Presence or absence of nausea
3. Episodes of vomiting and/or retching
4. Duration of nausea and vomiting and/or retching
5. Intensity of nausea by VAS
6. Eastern Cooperative Oncology Group (ECOG) assessment
7. McCorkle Symptom Distress Scale (Quality of Life [QOL])

*Safety:*  
Subject safety was monitored with the following assessments:

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1. Physical examination
2. 12-lead electrocardiogram (ECG) with rhythm strip
3. Vital signs (seated blood pressure, seated pulse and oral temperature)
4. Laboratory assessments
5. Adverse event (AE) monitoring
6. Concomitant medications

**Statistical Methods:**

Descriptive statistics were generated to summarize the demographic information and Baseline characteristics for each treatment group.

Due to the decreased sample size (464 reduced to 64), the planned interim analysis for the possibility of futility was not conducted. All statistical testing was performed using a two-sided test at a 0.050 level of significance.

*Efficacy*

The primary efficacy parameter, the number and percentage of total responders across Days 2-5 was analyzed using a logistic regression model with treatment and pooled center as covariates. The pairwise treatment group comparison between Dronabinol (Group D) and Ondansetron (Group O) was considered primary. The remaining pairwise comparisons were considered secondary analyses. The number and percentage of total responders were also summarized for each study day, although no statistical testing was performed for the by-study day analysis.

Continuous secondary efficacy parameters were analyzed for all pairwise comparisons using a two-way analysis of variance (ANOVA) model with treatment and pooled center as fixed factors. Chemotherapy status was defined in Amendment 3 (naïve versus non-naïve) but was inadvertently not collected in the CRF database. The study sites were contacted to confirm the status of the 64 subjects enrolled at the time of study closure and this information was added to the analysis database. Thus, the effect of covariate chemotherapy status was conducted as exploratory analysis only.

If the data were non-normally distributed (Shapiro-Wilk  $p < 0.001$ ), an ANOVA was performed using the ranked scores.

Categorical secondary efficacy parameters were analyzed for all pairwise comparisons using the Cochran-Mantel-Haenszel (CMH) test stratified by pooled center.

No adjustments were made for multiple comparisons.

An exploratory analysis was conducted to examine the effect of dronabinol on the day of chemotherapy (Day 1). All subjects received a standard pre-chemotherapy antiemetic regimen.

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Subjects in the active treatment groups also received a pre-chemotherapy treatment regimen that included dronabinol plus a post-chemotherapy dose of dronabinol. Efficacy analyses were conducted comparing the combined active treatment subjects to those subjects who received placebo. The parameters assessed in Day 1 data analyses were (1) total response, (2) complete response, (3) presence/absence of nausea, and (4) VAS intensity of nausea. Treatment group comparisons of first three parameters (categorical variables) were evaluated using Fisher’s exact test. P-values for the VAS nausea intensity scores were computed based on a Wilcoxon rank test. Descriptive statistics for Day 1 efficacy parameters were also summarized by treatment groups.

*Safety*

Adverse events and concomitant medications were summarized for each treatment group. Summary tables and subject listings were presented with markedly abnormal or out-of-range values for vital signs, laboratory parameters, physical examinations and body weight.

**Summary**

*Efficacy Results*

- The rate of total response of nausea and vomiting/retching in subjects given dronabinol was found to be comparable to, but not statistically significantly different from, the response of ondansetron alone or in combination with dronabinol in the treatment of delayed CINV (Days 2 through 5).
- A number of secondary efficacy assessments suggest that dronabinol treatment may be clinically comparable to, or even better than, ondansetron treatment (alone or with dronabinol) including reducing the episodes of vomiting/retching, reducing the occurrence of nausea, and reducing its intensity. Quality of life at Endpoint, measured by the McCorkle scale, was most improved in Group D compared to the other treatment groups. More shifts in ECOG (wellness) assessment scores from 1 to 0 occurred in subjects in Group D, but since more subjects in Group D had scores of 1 at Baseline, no firm conclusions can be drawn from this measure.
- Results from an exploratory analysis of Day 1 indicated that the combined active treatment group (Group D, Group O and Group DO), which received dronabinol in addition to the standard pre-chemotherapy regimen of dexamethasone and ondansetron plus a dose of dronabinol post-chemotherapy, was statistically significantly superior to Group P for the efficacy parameters of total response, presence of nausea, and intensity of nausea on the VAS.

*Safety Results*

The incidence of treatment-emergent adverse events (TEAEs) observed among the three active treatment groups was similar (71 to 88%) compared to 50% in Group P. TEAEs occurring in two or more subjects in each group were: diarrhea, asthenia and fatigue in Group D; headache, insomnia, hyperglycemia, chest pain and constipation in Group O; and dizziness, fatigue, and headache in Group DO. No TEAEs were reported by two or more subjects in Group P.

Group D had low incidence of CNS-related TEAEs compared to Group O and Group DO.

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Dizziness and fatigue occurred in all active treatment groups; the incidences of both were highest in Group DO.

One subject in Group P died from sepsis on Day 14 (post-study); the death was considered unrelated to study treatment by the Investigator. Five subjects experienced non-fatal SAEs; two subjects from Group D and one subject each from Group O, Group DO and Group P. All SAEs were considered unrelated to study medication by the Investigator; one SAE in Group D and the SAE in Group P occurred post-study.

Six subjects had non-fatal AEs that led to permanent discontinuation of study medication.

More subjects were from Group DO (three subjects; one with an SAE) than Group O (two subjects; one with an SAE), Group D (one subject) or Group P (no subjects).

Abnormalities in laboratory values and vital signs were not considered clinically important and were most likely due to the underlying cancer.

Date of the report: 06 MAY 2005