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<b>Proprietary Drug Name:</b> Marinol	<b>Generic Drug Name:</b> Dronabinol	<b>Condition:</b> Highly Active Antiretroviral Therapy (HAART)-related Nausea and Vomiting
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**Name of Sponsor/Company:**  
Solvay Pharmaceuticals

**Title of Study:**  
A Double-blind, Randomized, Parallel-group, Pilot Study of Oral Dronabinol versus Placebo in the Treatment or Prevention of Highly Active Antiretroviral Therapy (HAART)-related Nausea and Vomiting  
Protocol No.: S175.2.101

**Investigator(s):**  
20 Investigators randomized subjects in the study.

**Study Center(s):**  
29 sites received shipment of study medication; 25 sites screened 1 or more subjects.

**Publication (Reference):**

<b>Study Period:</b> 28 AUG 2003 (First Subject First Visit) – 22 APR 2005 (Last Subject Last Visit)	<b>Phase of Development:</b> Phase II
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**Objectives:**  
The primary objective of this study was to determine if dronabinol is effective in preventing or treating nausea induced by HAART in HIV+ (human immunodeficiency virus positive)/AIDS (acquired immune deficiency syndrome) subjects.

Secondary measures to assess the patient’s response to study drug included:

- a) Number of episodes of vomiting and/or retching
- b) Duration of nausea and vomiting and/or retching
- c) Intensity of nausea
- d) Appetite stimulation
- e) Body weight
- f) Quality of life – Multidimensional Quality of Life Questionnaire for Persons with HIV/AIDS (MQOL-HIV) survey
- g) Karnofsky Performance Status

**Methodology:**  
HIV+/AIDS subjects were divided into 2 cohorts. Cohort A included subjects who were non-adherent to prior HAART due to nausea and vomiting and/or retching, who discontinued or interrupted HAART due to nausea and vomiting and/or retching or who were currently on HAART and experiencing nausea and vomiting and/or retching. These subjects were required to resume or continue the HAART regimen that caused the nausea and vomiting and/or

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retching or any other regimen that was likely to cause this problem in order to participate in the study. Subjects in Cohort A who stopped prior HAART due to nausea and vomiting and/or retching resumed HAART at baseline, Day 1 (after titration). Cohort B included subjects starting or switching to HAART that included a protease inhibitor (preferentially a ritonavirboosted protease inhibitor (PI) or zidovudine (AZT)).

Subjects in each cohort were randomly assigned to receive either dronabinol or placebo.

HAART was administered on Day 1 (except for subjects in Cohort A who had already received it) and subjects continued study medication for a 2-week period (Titration/Treatment Phase).

Titration/Treatment Phase (Weeks 1-2): After randomization, all subjects began treatment with 2 capsules twice daily (5 mg BID in the dronabinol group; 10 mg/day). Subjects randomized into either treatment group could increase the dose of study medication based on the degree of nausea and vomiting and/or retching by 1 or 2 capsules daily (2.5 mg or 5 mg in the dronabinol group) to a maximum daily dose of 16 capsules (8 capsules by mouth BID; 40 mg/day in the dronabinol group). The dose could also be decreased by 1 or 2 capsules daily, based on the subject's tolerability. The minimum dose was 1 capsule daily (2.5 mg daily for the dronabinol group). If the first dose on Day 1 was not tolerated, the second dose on Day 1 could be decreased to 1 capsule or omitted entirely. In the event of an unequal number of capsules per dose, it was recommended that the larger dose be taken in the evening. Once an optimum dose was reached, subjects were encouraged to maintain that dose for the remainder of the study. All subjects discontinued study medication at the end of Week 2.

Post-treatment follow-up (Week 3): Subjects returned to the clinic at Week 3 for post-treatment safety assessments.

Clinic visits occurred at screening (up to 14 days prior to randomization), randomization (i.e., Day 1 of Titration/Treatment Phase), weekly at the end of Weeks 1 and 2, and at post-study Week 3. The total duration of double-blind therapy was 2 weeks. All subjects had the option of receiving promethazine or prochlorperazine as a rescue medication to treat intolerable nausea and vomiting and/or retching during double-blind treatment. Subjects who required rescue medications were discontinued from the study at that point.

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**Number of Subjects (Planned, Consented, Randomized and Analyzed):**

A total of 58 subjects were planned for Cohort A; Cohort B had no pre-planned sample size. A total of 131 subjects consented, of which 103 were randomized (77 to Cohort A and 26 to Cohort B). The number of subjects in Cohort A surpassed expectations due to several subjects still in screening at the time enrollment was closed, who were given the opportunity to be randomized into the study.

**Diagnosis and Main Criteria for Inclusion:**

Males or females, 18 to 70 years of age, with documented HIV infection or AIDS meeting 1 of the following criteria:

- a) adherence to prior or current HAART was or is being compromised, or HAART was discontinued/interrupted due to nausea and vomiting.
- b) beginning HAART or switching from a regimen that did not produce significant nausea and/or vomiting to a regimen with AZT or a protease inhibitor (with or without low dose ritonavir).

**Test Product, Dose and Mode of Administration:**

Dronabinol 2.5 mg softgel, administered orally; dose range 2.5 mg/day to 40 mg/day (1-16 capsules/day).

**Duration of Treatment:**

2 weeks

**Reference Therapy, Dose and Mode of Administration:**

Placebo softgels, administered orally at a dose range 1 to 16 capsules/day.

**Criteria for Evaluation:**

Efficacy:

The absence of nausea as indicated by a visual analog scale (VAS) score < 5 mm was the primary efficacy measure and reported through the Quintiles Interactive Voice Response System (IVRS) and written diary. The primary efficacy variable was the rate of complete response of nausea at Week 2 using last observation carried forward (LOCF) data. The complete response of nausea at a target week was defined as absence of nausea at that week.

The primary efficacy parameter was originally chosen to address the preventive effect of dronabinol, however, study design limitations made this objective unattainable.

- In the original design (Pre-Amendment 2), randomization occurred prior to titration; subjects were then treated on dronabinol or placebo for 2 weeks in order to achieve a VAS < 5 mm at Baseline (the end of titration); and subjects continued on the same treatment for the 4-week post-baseline phase. This design introduced a selection bias of subjects who could be “treated” for each treatment group, so treatment differentiation was unattainable.

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- The new design (Amendment 2), improved on the original design by defining baseline prior to randomization, however, only one subject was confirmed as having a VAS < 5 mm at baseline; and 42% had a missing baseline.
- At the time of Amendment 2, the primary efficacy parameter should have been modified to address the new objective of treatment of HAART-related nausea and vomiting; and the change in the subject population should have led to the elimination of the preventive objective. Since this was a pilot study, additional exploratory analyses (not described in the SAP) were considered to summarize the data and to address the objective of treatment.

Secondary assessments included:

1. Number of episodes of vomiting and/or retching
2. Duration of nausea and vomiting and/or retching
3. Intensity of nausea by VAS and IVRS phone diary
4. Appetite stimulation by written VAS and IVRS phone diary
5. Body weight
6. Karnofsky Performance Status
7. Quality of Life Modified MQOL-HIV survey

The secondary efficacy parameter, intensity of nausea by VAS, appears the most relevant to assess the treatment effect of dronabinol, however, 25% to 40% of the Cohort A subjects had zero intensity at baseline, meaning there was no opportunity to improve.

Exploratory analyses were performed on the Post-Amendment 2 Cohort A VAS  $\geq$  5 mm subgroup to explore the potential effects of dronabinol in the treatment of HAART-related nausea.

- Only one subject in the Pre-Amendment 2 design met the VAS criterion.
- Several subjects (about 42%) had a missing baseline VAS Post-Amendment 2 and were not included in this analysis, so interpretation of the exploratory analyses is limited.
- Intensity of nausea by VAS was considered as the most relevant parameter to assess the treatment effect of dronabinol on this exploratory population.

### Safety

The safety of the subject was monitored prior to, during and at the conclusion of the study using the following assessments:

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1. Physical examination
2. Mini-Mental Status Examination (MMSE)
3. Vital signs
4. 12-lead electrocardiogram (ECG)
5. Clinical laboratory assessments including liver function tests, serum electrolytes, complete blood count with differential, platelet count, prothrombin/partial thromboplastin time, urinalysis, and urine drug screen
6. Adverse event reports, with special attention to central nervous system (CNS) adverse events (AEs) as a subgroup of AE analysis
7. Concomitant medications
8. ACTG Adherence Follow-up Questionnaire from the Adult AIDS Clinical Trial Group (AACTG)

**Statistical Methods:**

Primary efficacy

The efficacy measurements for subjects in Cohort A and B were analyzed and evaluated independently, therefore, multiple test adjustment was not required. The analysis of Cohort B was for exploratory purposes only. The Cochran-Mantel-Haenszel (CMH) test with center as control variable (strata) was performed to test the treatment effect at each week. The primary efficacy results were based on the CMH-test on Intent-to-Treat (ITT) efficacy subject population at Week 2 using LOCF data. The analysis based on the observed cases (OC) data at Week 1 was supportive. For each treatment group, descriptive statistics included: n, percentage, and exact 95% two-sided confidence interval. A 95% two-sided confidence interval for the difference of the proportions between 2 treatments was also provided.

Secondary efficacy: All secondary efficacy variables were measured daily by IVRS, including the episodes of vomiting and/or retching, duration of nausea and vomiting and/or retching, and summed over each week. Intensity of nausea obtained by VAS (through written diary and IVRS) was analyzed weekly. These secondary efficacy variables and other secondary efficacy variables including the change from baseline of Karnofsky Performance Status, MQOL-HIV survey, body weight, and appetite stimulation by written VAS and IVRS phone diaries, were analyzed. The statistical analysis used analysis of variance (ANOVA) on LOCF data of ITT efficacy subject population at Weeks 1 and 2. The baseline value was the measurement for baseline (Day 1). The efficacy data collected at the follow-up period was also summarized.

The statistical model for the ANOVA had treatment and center as fixed factors, if the normal assumption was supported by the data. Without normality, a non-parametric analysis was performed on the rank transfer data. Descriptive statistics of the secondary efficacy variables

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including: n, mean, standard deviation, median, minimum, and maximum were provided. A two-way analysis of covariance model was utilized (ANCOVA) for the parameters with a baseline (intensity of nausea, body weight, KPS, Modified MQOL-HIV survey).

All statistical testing (two-sided) was analyzed at the  $p < 0.05$  level of significance.

### **Exploratory Analyses**

The Post-Amendment 2 (Post-A2) Cohort A subjects with baseline nausea intensity VAS scores  $\geq 5$  mm were the subgroup population chosen for post-hoc exploratory analyses. Although an exploratory population, it was considered a valid population upon which to draw any inferences on the effects of dronabinol in the treatment of HAART-related nausea and vomiting. The efficacy discussion in the report focuses on this subgroup population as well as the entire Cohort A.

All ad hoc efficacy analyses were performed using this subgroup of Cohort A. Additionally, the incidence of AEs by treatment group was evaluated for this subgroup. However, for the primary safety assessments all subjects from the combined Cohorts A and B across both amendments were used.

### **Summary**

Efficacy Results:

- Results of the primary efficacy parameter as originally defined in the SAP (complete response of nausea in Cohort A at Week 2) did not indicate anti-nausea activity in either dronabinol or placebo groups. Similarly secondary objectives on Cohort A did not show differences between treatments. As discussed in the synopsis section *Criteria for Evaluation*, study design limitations made these objectives unattainable.
- Greater changes from baseline intensity of nausea scores in the Subgroup of Cohort A subjects were noted in the dronabinol treatment group on both weeks compared to the placebo treatment group. A decrease of 15.3mm in nausea intensity scores from baseline at Week 1 in dronabinol-treated subjects showed a favorable trend relative to that of placebo-treated subjects where a decrease of 5.9mm was noted ( $p=0.073$ ). The largest decrease in mean nausea intensity scores from baseline in dronabinol-treated subjects was 27.9mm at Week 2 as compared to placebo-treated subjects, where a decrease of 14.5mm was noted ( $p=0.148$ ).
- The Subgroup of Cohort A had less frequent episodes of vomiting/retching at Week 1 in the dronabinol-treated subjects with a mean of 7.4 as compared to a mean of 9.4 in the placebo-treated subjects ( $p=0.310$ ). At Week 2, an apparent trend developed where

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dronabinol-treated subjects remained relatively unchanged with a mean of 7.2 as compared to a mean of 12.9 in the placebo-treated subjects (p=0.056).

- In the MQOL-HIV survey nausea item, the Subgroup of Cohort A subjects receiving dronabinol had larger reductions in their nausea scores of -1.4, compared to -0.6 for placebo.
- Additional secondary efficacy parameters on the Subgroup of Cohort A, such as duration of nausea and vomiting/retching; appetite stimulation; body weight; and the KPS showed no differences between treatments.

Safety Results:

- Dronabinol was well tolerated at the dose levels used in the study. The incidence of TEAEs in dronabinol-treated subjects (54%) was only slightly higher than that of placebo-treated subjects (44%). The principal difference in TEAEs was the higher incidence of CNS related events such as dizziness (23%), somnolence (8%), memory impairment (4%) and vertigo (4%) in the dronabinol group. There were no SAEs or deaths reported. A total of two (4%) subjects in the dronabinol treatment group had TEAEs that led to discontinuation of study medication.
- No clinically significant differences between treatment groups were noted in physical examinations, mental status, vital signs, electrocardiogram, clinical laboratory assessments, concomitant medications, or adherence to HAART regimens.
- ACTG adherence (percentages) for Cohort A and the Subgroup of Cohort A were maintained at a high level in both dronabinol- and placebo-treated subjects over the course of treatment. Also, no notable differences in overall adherence were noted between treatment groups in Cohort A and the Subgroup of Cohort A.

Date of the report: 20 FEB 2006