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Sponsor/Company : sanofi-aventis **Drug substance :** Modafinil		**Study Identifier :** NCT00917748 **Study Code :** DOCET_L_04203	
Title of the study:	A Prospective, Randomised, Double-Blind, Placebo-Controlled Phase III Study of Modafinil to Improve Fatigue and Quality of Life in Patients Treated with Docetaxel-Based Chemotherapy for Metastatic Breast or Prostate Cancer		
Study centers:	26 centers, Australia-wide		
Study period: Date first patient enrolled: 16-Jun-2009 Date last patient completed: 23-Mar-2011			**Phase of development:** III
Objectives:	Primary: o To determine the efficacy of modafinil in the reduction of fatigue in patients with metastatic breast or prostate cancer undergoing docetaxel-based chemotherapy. Secondary: o To determine the effect of modafinil on quality of life (QoL) during docetaxel-based chemotherapy. o To determine the effect of modafinil on patients' physical activity level, functional status, number of chemotherapy cycles tolerated, sleep disturbance and depression, during docetaxel-based chemotherapy. o To investigate the impact of tumour type, patient physical activity level, functional status, sleep disturbance and depression on the efficacy of modafinil at improving fatigue and quality of life during docetaxel-based chemotherapy. o To determine the safety and tolerability of modafinil during docetaxel-based chemotherapy.		
Methodology:	A Prospective, Randomised, Double-Blind, Placebo-Controlled Phase III Study. Patients receiving docetaxel chemotherapy will be randomised to one of 2 arms: Arm 1: best supportive care plus modafinil 200 mg mane daily. Arm 2: best supportive care plus placebo mane daily. Best supportive care will include a patient fact sheet provided to each study patient outlining supportive care measures to minimise their fatigue / asthenia (e.g., short daytime naps, limit alcohol, maintain a balanced lifestyle including exercise, fluid intake advice etc).		
Number of patients:	Original: 138 Amended: 82	Enrolled: 88 Screened: 86 Randomised: 84	Treated: 83
Evaluated:	Efficacy: 83 patients	Safety: 83 patients	

Diagnosis and criteria for inclusion:	Study Population Patients with metastatic breast or prostate cancer, and docetaxel chemotherapy-related fatigue (MD Anderson Symptom Inventory MDASI fatigue score ≥ 4 and SPHERE-SOMA (Somatic and Psychological Health Report) subscale score ≥ 3 during the previous chemotherapy cycle). Patients must have been treated with at least two cycles of chemotherapy and scheduled to commence their third, fourth or fifth cycle of docetaxel-based chemotherapy. There must be an intention to treat the patient for at least two further cycles of chemotherapy during the study. Inclusion Criteria: 1) Age ≥ 18 years. 2) Willing and able to provide written informed consent. 3) Treatment with q3w (every three weeks) docetaxel-based chemotherapy for metastatic breast or prostate cancer at a minimum dose of 50 mg/m^2. 4) Completed at least two cycles of chemotherapy and intention to treat the patient with at least two further cycles of docetaxel-based chemotherapy. 5) Fatigue ≥ 4 on the MDASI fatigue assessment scale during the previous docetaxel chemotherapy cycle. 6) SPHERE somatic (SOMA) subscale score ≥3. 7) Worsening of fatigue after commencement of docetaxel chemotherapy. 8) Haemoglobin (Hb) ≥ 10 g/dL within two weeks before randomisation. Exclusion Criteria: 1) Unable to complete the MDASI fatigue assessment scale or FACIT-F QoL (Functional Assessment Of Chronic Illness Therapy-Fatigue Quality of Life) survey. 2) Require docetaxel chemotherapy dose reduction to less than 50 mg/m^2. 3) History of chronic fatigue condition. 4) Uncontrolled hypertension (blood pressure ≥ 150/90 mm Hg) 5) Known hypersensitivity / intolerance to modafinil or any of the excipients. 6) Pregnant women. 7) Psychological, familial, sociological, or geographical conditions that do not permit treatment or medical follow-up and / or prohibit compliance with the study protocol. 8) Any serious concomitant illness that, in the opinion of the Investigator, would preclude a patient from participating in the study (e.g. patients who are medically unstable, including but not limited to, active infection, acute hepatitis, gastrointestinal bleeding, uncontrolled cardiac arrhythmias, interstitial lung disease, inflammatory bowel disease, uncontrolled angina, uncontrolled hypercalcaemia, uncompensated congestive cardiac failure, uncontrolled diabetes, dementia, seizures or superior vena cava syndrome). 9) Non-English speaking.
Investigational product: Dose: Administration:	Modafinil Two 100 mg capsules (200 mg total), once daily – mane (before noon). To avoid potential drug interactions between docetaxel, steroid premedications and study medication, study medication was discontinued for three days before and after each docetaxel infusion. Oral

Duration of treatment: Minimum of 9 weeks Maximum of 12 weeks	**Duration of observation:** Screening = 3 weeks Post treatment = 3 weeks

Reference therapy: Dose: Administration:	Placebo (lactose) capsules Two placebo capsules, once daily – mane (before noon). To avoid potential drug interactions between docetaxel, steroid premedications and study medication, study medication was discontinued for three days before and after each docetaxel infusion. Oral
Criteria for evaluation: Efficacy: Safety:	 Daily fatigue scores (measured using the MDASI) and weekly QoL scores (assessed using the FACIT-F QoL survey) were collected at baseline (randomisation) and during the entire study period for patients in both treatment arms (modafinil or placebo). The somatic subscale of the SPHERE questionnaire (SPHERE-SOMA) was used to measure fatigue at screening and immediately before each chemotherapy treatment cycle (infusion). The PSQI (Pittsburgh Sleep Quality Index) and SF-36 questionnaires were used to assess sleep quality and functional status, respectively, at baseline and immediately before each chemotherapy treatment cycle. Data collection with the MDASI, FACIT-F, SPHERE-SOMA, PSQI and SF-36 scales were continued until the completion of the study (i.e. final study visit). The HAD (Hospital and Anxiety Depression) score (to assess presence of depression) was collected at baseline and upon completion of the study. Patient activity level was determined by calculation of weekly METs score at baseline and study completion. To monitor Adverse Events, patients were contacted daily by telephone for the first three days of treatment with modafinil or placebo during the first cycle of chemotherapy. Patients were also monitored at study visits every three weeks. At each visit a physical examination was completed and full blood count data recorded; blood pressure, heart rate, Adverse Events and concomitant medications were also recorded.
Statistical methods:	The primary efficacy endpoint was the area under the curve (AUC) captured by a plot of MDASI fatigue score versus time (days), during the first seven days of study medication treatment, ie days 3 to 10 after docetaxel treatment. The units of measurement for the AUD were 'score days'.For each patient, the AUC of each of the first two cycles of docetaxel-based chemotherapy were used. If a patient completed only one cycle of chemotherapy during their enrolment in the study, the patient's MDASI fatigue score AUC for this single cycle was used. Analyses of the primary endpoint and most secondary endpoints were undertaken overall for two cycles with additional analyses by tumour type, by cycle and by tumour type and cycle to investigate possible interactions. These analyses were repeated over the four cycles. For each analysis a mixed model was fitted to the endpoints estimated for each patient. For example, the MDASI $AUC_{3\text{-}10}$, MDASI $AUC_{3\text{-}18}$, FACIT-F score each week and the SF-36 score for each subscale at each visit. The original sample size required to achieve the primary endpoint was estimated with the aim of averaging the Area under the Curve (AUC) of the MDASI daily fatigue scores over two cycles of chemotherapy for each patient. Thus allowing for a 5% drop-out rate during the study, 138 patients (modafinil arm: n = 92; placebo arm: n = 46) were required to be randomized. Subsequent to the release of the protocol, the statistical analysis plan (SAP) was developed which refined the analysis method for the primary endpoint to include the AUC for each cycle separately and to model the repeated measures nature of the data appropriately. As a result, assuming that each patient completed two cycles of chemotherapy, the MDASI fatigue score AUC was calculated for each cycle, the standard error after accounting for the repeated measurements would be 6.3 and the correlation between the two AUC measurements within each patient 0.75, a sample size of 77 patients (modafinil arm: n = 51; placebo arm: n = 26) would provide 80% power to detect a difference of four units between the mean AUC for each treatment group. This was believed to reflect the originally aimed for 10% relative difference in mean "score days" between the two treatment groups. This assumption was based on a two-sided significance level of $\alpha = 0.05$. Allowing for a 5% drop-out rate during the study, the sample size was reviewed to requiring 82 patients (modafinil arm: n = 55; placebo arm: n = 27) to be randomised.

Summary:	A total of 88 patients from 25 centres signed a consent form but 2 of these patients withdrew prior to being screened for eligibility. 84 patients were randomised. There were no statistically significant differences between treatments in the quality of life measurements, physical activity level, functional status or the number or chemotherapy cycles tolerated. There were no significant safety signals detected.
Efficacy results:	The difference between modafinil and placebo for MDASI AUC_{3-10} overall was not statistically significant at -3.7 (35.9 vs 39.6 for modafinil and placebo respectively, p=0.15). There was an indication that the difference between treatments was not consistent across cycles (interaction p=0.05). Patients in the modafinil arm had significantly less fatigue in cycle 2 compared with placebo (33.7 vs 40.1 score days for modafinil and placebo respectively, p=0.03) where they were almost equal in cycle 1. The per-protocol analysis supported this finding. A similar pattern was seen in the analysis over four cycles with no difference between treatments in cycle 1 followed by a difference between treatments at cycle 2 that remained reasonably consistent across the remaining cycles. There was no relationship between patient physical activity level, functional status, sleep disturbance or depression at baseline on the effect of modafinil at improving fatigue during docetaxel based chemotherapy as measured by MDASI AUC_{3-10} over two cycles. No statistically significant differences between treatment arms were observed in the analysis of the MDASI AUC_{3-18} for the first two-on-study cycles, nor the analysis for all on-study cycles although in most instances the differences observed were in favour of the modafinil arm and the pattern over time was consistent with the AUC_{3-10} results. There were no statistically significant differences in daily MDASI fatigue scores. However, exploratory analysis supported the view that fatigue for subjects in the modafinil arm was generally lower than in the placebo arm. There was no significant difference in maximum MDASI fatigue score recorded on days 3 to 18 of each cycle. However, there was a significant difference in the time taken to reach the maximum score over both the two-cycle analysis and the four-cycle analysis (1.4 days longer on modafinil, p=0.02 over two cycles and 1.0 day, p=0.04 over four cycles) Results were generally similar for both tumour types. Where a significant difference may have occurred between treatments within patients with breast cancer results should be treated with care due to the small number of breast cancer patients. There were no statistically significant differences between treatments in the quality of life measurements overall for the two-cycle analyses or the four-cycle analyses. There was a possibility of a difference at the end of cycle 1 in the role-physical subscale in favour of modafinil (difference = 4.3, 95% CI = 1.1 to 7.4, p=0.01). There was no statistically significant difference in physical activity level as measured by METs overall (end of study minus baseline score; difference = 12.1, 95% CI = -5.8, 30, p=0.18). However there was a statistically significant improvement in physical activity for modafinil patients in the prostate cancer group as measured by METs (difference = 23, 95% CI = 3.3 to 42.6, p=0.02). There was no correlation between the change in physical activity and the change in fatigue as measured by the MDASI fatigue score. There were no significant differences in functional status, the number of chemotherapy cycles tolerated, sleep disturbance and depression during docetaxel-based chemotherapy.

Safety results:	There were no significant safety signals detected. With a 2:1 randomisation it would be expected that approximately twice as many patients would experience treatment emergent adverse events and discontinue treatment due to their adverse event, as was seen in this study. There were three deaths in the study, all were in the prostate cancer group and none were related to study treatment (docetaxel or modafinil). Patients were on the placebo arm. One was a result of disease deterioration, one from renal failure and one from disease progression. There were no differences observed in clinical laboratory values over time, vital signs, physical findings or the number of blood transfusions required.
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