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PROPRIETARY DRUG NAME®/GENERIC DRUG NAME: Chantix® /Champix®/ Varenicline tartrate

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS: See United States Package Insert (USPI)

NATIONAL CLINICAL TRIAL NO.: NCT00889720

PROTOCOL NO.: A3051113

PROTOCOL TITLE: A Multicenter, Open Label Study to Investigate the Feasibility and Efficacy of a Smoking Cessation Program with Varenicline in Patients Undergoing Elective Surgery

Study Centers: 2 centers took part in the study, 1 center in France and 1 center in Italy.

Study Initiation Date and Completion Date: 03 November 2009 to 29 July 2010

Phase of Development: Phase 4

Study Objectives:

- Assess the feasibility of conducting a multicenter prospective study involving smoking cessation treatment, preplanned and scheduled surgery and collection of data on surgical site infections (SSIs) and other postoperative complications.
- Generate data on rates of SSIs and other postoperative complications in patients undergoing elective orthopaedic, plastic, general and vascular surgery.
- Assess the practicality and utility of 3 separate instruments in recording data on SSI and in assessing and grading SSIs and of a further instrument in grading other postoperative complications.
- Assess the efficacy of varenicline and smoking cessation advice to enable cessation of smoking for the 7-day period preceding hospital admission in subjects undergoing elective surgery.
- Assess the efficacy of varenicline and smoking cessation advice to enable smoking cessation at other time points in subjects scheduled for elective surgery.
- Assess the efficacy of varenicline and smoking cessation advice to enable subjects to reduce the number of cigarettes or cigarillos they smoke by >50% in the 7 days preceding hospital admission compared with baseline.

- Assess the efficacy of varenicline and smoking cessation advice to enable smoking reduction at other time points in patients scheduled for elective surgery.
- Assess the safety and tolerability of a 12-week course of varenicline in subjects scheduled for elective surgery.
- Enable exploratory analyses of the influence of smoking cessation on postoperative outcomes; in particular to evaluate the optimal timing of smoking cessation prior to surgery in relation to wound healing.

METHODS

Study Design: This pilot study was an open label, multicenter clinical study that planned to recruit 100 subjects to investigate the feasibility and efficacy of a future smoking cessation study with varenicline in smokers aged 18 or over undergoing planned elective surgery.

After Screening and an initial week of dose escalation all subjects were to receive varenicline 1 mg twice daily (BID) for 11 further weeks of study drug treatment (total duration of treatment with study drug: 12 weeks) in accordance with the approved prescribing information. The planned total duration of the study was 26 weeks (excluding Screening).

For the first 12 weeks of the study, subjects were asked to record the number of cigarettes/cigarillos smoked and the use of any other nicotine products in a diary. The investigator administered the Nicotine Use Inventory (NUI) at the planned visits.

Subjects were to return for clinic visits at Weeks 2 and 4. At these visits, subjects received up to 15 minutes of verbal advice on smoking cessation. An exhaled carbon monoxide (CO) test was also performed. If admission for surgery was not anticipated to occur before Day 66 (Week 8 +10 days) or if there was a need to provide new drug supplies, subjects were to return for an additional clinic visit at Week 8.

Elective surgery was to be planned to occur at 8 weeks ± 10 days after the start of study drug treatment. On admission for elective surgery subjects were asked about their smoking status and exhaled CO was measured. Subjects could temporarily stop study drug (while nil by mouth) but were to resume varenicline after surgery when it was considered safe to take oral medication. Subjects were to be assessed for wound healing and the presence of surgical wound infection and other postoperative complications on at least 2 separate occasions, once during Days 1 to 3 and once during Days 6 to 10 postsurgery and again at the end of Week 12. Regarding more general postoperative complications, the classification systems developed by Clavien and published by Dindo et al and an instrument used by Lindström et al were to be used. Subjects were to be assessed again at the scheduled end of study drug treatment (Week 12), and finally at 26 weeks after start of study drug treatment (Week 26), by which time the subjects were to have been off study drug for 14 weeks. Smoking status was to be re-assessed at each of these visits, and exhaled CO was to be measured.

Number of Subjects (Planned and Analyzed): The study planned to enroll approximately 100 smokers. As recruiting smokers scheduled for elective surgery within a reasonable

timeframe would not be feasible for a larger future study, study recruitment was halted prematurely after 16 subjects had been enrolled.

Diagnosis and Main Criteria for Inclusion: The study included male or female cigarette or cigarillo smokers aged 18 or over who were scheduled to undergo planned elective surgery expected to produce a scar at least 3 cm long, and who were motivated to stop smoking before surgery. Subjects had to have smoked an average of at least 10 cigarettes or cigarillos per day during the month prior to the screening visit and during the past year, with no period of abstinence greater than 3 months in the past year.

Study Treatment: Commercial supplies of the study drug were provided locally. All subjects received treatment with varenicline tartrate. Varenicline was administered orally with water. During the first week of the study, tablets containing 0.5 mg varenicline tartrate and during the remaining 11 weeks of the study, tablets containing 1 mg varenicline tartrate were to be administered in accordance with the approved prescribing information. The investigators had the option to reduce the dose to 0.5 mg BID if the subject was unable to tolerate the 1 mg BID regimen. Subjects could temporarily stop study drug during the surgery (while nil by mouth) but were to resume varenicline after surgery when it was considered safe to take oral medication.

Efficacy Evaluations: Nicotine dependence was assessed at Screening using the Fagerström Test for Nicotine Dependence. For the first 12 weeks of the study (apart from days spent entirely in hospital) subjects were asked to record an estimate of the number of cigarettes they had smoked each day in a diary. The subject's end-expiratory exhaled CO level was measured at all visits except Screening, Day 0 and Days 1 to 3 postsurgery to confirm smoking abstinence. The NUI was used to collect the information regarding cigarettes, cigarillos and other nicotine-containing products used during both the treatment and follow up phases.

The healing of the surgical site wound and the possible presence of infection was assessed postoperatively at Days 1 to 3, Days 6 to 10 and the visits at Weeks 12 and 26 to assess for delayed wound healing or late or persisting wound infection. At the same time points, SSI and wound healing was assessed using the Centers for Disease Control (CDC) 1992 Definition for SSIs; wounds were assessed using the Southampton Wound Assessment Scale and the ASEPSIS Wound Grading Scale (ASEPSIS was used at the site at Hôpital Pitié-Salpêtrière only); and postoperative complications were assessed using a scale developed by Clavien and published by Dindo et al and a classification used by Lindström et al. In addition, surgical outcomes identified by the Otago surgical audit were collected.

Safety Evaluations: All adverse events (AEs; serious and non-serious) were recorded from the time the subject had taken at least 1 dose of study drug up to 28 days post end of treatment. From 28 days after the end of treatment up to Week 26, all AEs were recorded that were linked to the wound or clinical study procedures and/or were considered important in the judgment of the investigator.

Subjects were screened for symptoms of depression at entry to the study and at every scheduled visit using the depression scale of the Patient Health Questionnaire (PHQ-9). The

Columbia Suicide-Severity Rating Scale (C-SSRS) was used to identify and assess any potentially suicidal ideation or behavior at Screening (and at later visits if needed).

At Screening, the medical history was collected, and a physical examination, an electrocardiogram, blood hematology, biochemistry and urinalysis (dipstick) were performed. Pulse and blood pressure (BP) were collected at every scheduled visit. A urine pregnancy test was performed only in women of childbearing potential at Screening, start of treatment, and 12 weeks after start of treatment.

Statistical Methods: Both the Full Analysis Set (FAS) and the safety analysis set (designated as 'all subjects' in the demography and safety results) were defined as all subjects who took at least 1 dose (including partial doses) of study medication. Therefore, for this study, the safety analysis set is identical to the FAS. The surgical population was defined as the subset of the FAS which included all subjects who received their planned surgery within the study period.

Due to the termination of study recruitment after enrolment of 16 subjects only selected efficacy and key safety data were reported.

RESULTS

Subject Disposition and Demography: Subject disposition is presented in Table 1.

Table 1. Subject Disposition

Number of Subjects	Varenicline
Screened	16
Assigned to study treatment	16
Treated	16
Completed treatment	8
Discontinued from the study - relation to the study drug not defined [1, 2]	8
No longer willing to participate in the study	4
Other reasons [3]	4

[1] Four discontinuations from the study occurred during the active treatment phase and 4 discontinuations during non-treatment follow-up.
[2] One additional subject discontinued the treatment, but not the study.
[3] Reasons for other discontinuations from study included not being able to adhere to the timelines and/or visits and postponement of surgery.

All 16 treated subjects were analyzed for safety. Twelve subjects were included in the surgical population.

Most subjects in the study were White. The mean age of male subjects (N = 9) and female subjects (N = 7) in this study was 45.2 years and 53.7 years, respectively. The mean weight of males and females was 83.0 kg and 66.8 kg, respectively, and the mean height was 170.9 cm and 157.9 cm, respectively.

Efficacy Results: For 12 of the 16 treated subjects, surgeries were performed. Note that not all assessments were performed for all subjects at all timepoints.

None of the 12 subjects which comprised the surgical population were fully compliant, ie they failed to fulfill all of the following criteria even though they may have fulfilled most of them: completing 12 weeks of varenicline therapy, undergoing surgery 8 weeks ± 10 days after start of treatment with varenicline, or having evaluations of wound infection 1 to 3 days postsurgery and 6 to 10 days postsurgery.

Nine of 12 subjects were responders in the 7-day point prevalence for abstinence from cigarette smoking (based on the NUI) and other nicotine use upon hospital admission and at Weeks 12 and 26. Three subjects were non-responders at all timepoints; none of these discontinued their treatment with varenicline early but 2 of these subjects were withdrawn during the post-therapy follow-up period.

None of the 12 subjects had SSIs postoperatively and at Weeks 12 and 26 as classified by the 1992 CDC definition. Due to satisfactory wound healing in all subjects, no swaps were taken and microbiological assessment was not necessary.

For 8 of 12 subjects, wound healing was assessed postoperatively and at Weeks 12 and 26 as normal with the Southampton Wound Assessment Scale. Two subjects had a grade of Ia at 1 timepoint, 1 subject had a grade of Ia at 1 to 3 days postsurgery and a grade of IIb at 6 to 10 days postsurgery, and 1 subject had a grade of IIa at 6 to 10 days postsurgery.

For 8 of 8 subjects at Weeks 12 and 26 using the ASEPSIS wound grading scale, infections were categorized as healing satisfactorily (only assessed in subjects at the site at Hôpital Pitié-Salpêtrière).

Eight of 12 subjects had no postoperative complications using the scale developed by Clavien and published by Dindo et al. For 4 subjects, postoperative complications occurred: for 2 of these subjects postoperative complications were of Grade I, for 1 subject of Grade II, and for 1 subject of Grade I and Grade IIIB.

Ten of 12 subjects had no postoperative complications using the Lindström classification system. For the remaining 2 subjects, postoperative complications were small bowel obstruction (1 subject) and hypocalcemia (1 subject). Both complications were related to the preceding surgery and not to the study drug.

A potential relationship of smoking status (responders versus non-reponders) with SSIs, wound healing outcomes, and postoperative complications could not be observed due to the low numbers of subjects.

Safety Results: Nine subjects experienced 28 all-causality treatment-emergent AEs; of those, 15 AEs in 8 subjects were treatment related. All treatment-emergent AEs resolved. Three subjects had severe treatment-emergent AEs (all causalities); for 1 of these 3 subjects the severe AEs (Nausea and Vomiting) were assessed as related to treatment.

The most frequent treatment-emergent AEs (occurring in more than 1 subject) are summarized in Table 2.

Table 2. Incidence of All-Causality and Treatment-Related Treatment-Emergent Adverse Events Occurring in More Than 1 Subject by Preferred Term, All Subjects

	Varenicline N = 16	
Number of Subjects	**All Causalities**	**Treatment Related**
Insomnia	3	3
Nausea	3	3
Decreased appetite	2	2
Vomiting	2	1

N = number of treated subjects.
Preferred terms were ordered by descending frequency of all-causality preferred terms. Subjects were counted only once per treatment in each row. Includes data up to 30 days after last dose of study drug.

One subject discontinued varenicline treatment due to AEs Dyspepsia and Insomnia, but remained in the study. Both AEs were moderate in severity and were assessed as treatment related.

Two subjects experienced AEs that led to dose reductions (severe Nausea and mild Decreased appetite in 1 subject and mild Mental disorder [investigator term 'change in ideation, non-severe mental disorder'] in another subject). All of these AEs were assessed as treatment related.

One subject experienced a treatment-emergent serious adverse event (SAE; Intestinal occlusion) following previous abdominal surgery. An additional subject experienced an SAE (Abdominal pain) that was not treatment-emergent as it occurred after the 30-day lag window. Both SAEs were assessed as severe, not related to varenicline treatment, and resolved.

There were no deaths in this study.

For none of the subjects was any suicidal ideation or suicidal behavior detected by clinical assessments including the using administration of the C-SSRS.

CONCLUSIONS:

- Due to slow recruitment in this study, conducting a further multicenter prospective study involving smoking cessation treatment in patients undergoing preplanned or scheduled surgery and collection of data on SSIs and other postoperative complications is not considered feasible. Also, none of the 12 subjects who had surgeries were fully compliant with the study protocol.

- The practicability and utility of the instruments used in this study to assess wound infections, wound healing, and postoperative complications could not be evaluated due to the low number of recruited subjects.

- The efficacy of varenicline and smoking cessation advice to enable cessation of smoking for the 7-day period preceding hospital admission in subjects undergoing elective surgery was assessed; 9 of 12 subjects having surgery were responders in the 7-day point prevalence for abstinence from cigarette smoking and other nicotine use upon hospital admission and at Weeks 12 and 26. A possible relationship of smoking status (responders versus non-responders) to SSIs, wound healing outcomes, and postoperative complications could not be observed due to the low number of subjects (especially of non-responders). Other planned efficacy analyses could not be performed.

- Varenicline treatment in 16 subjects was well-tolerated and did not raise any safety concerns. Twenty eight treatment-emergent AEs were recorded for 9 subjects, 15 of these were related to treatment in 8 subjects. No subject died in this study. There were 2 subjects with SAEs; for 1 of these subjects, the SAE was not treatment emergent. Both SAEs were not related to treatment. Three subjects had severe treatment-emergent AEs (all causalities); for 1 of these 3 subjects the severe AEs (Nausea and Vomiting) were assessed as related to treatment. One subject discontinued the treatment due to AEs, and 2 subjects reduced their varenicline dose due to AEs. Using the C-SSRS, for none of the subjects was any suicidal ideation or suicidal behavior detected.