Effects of Varenicline in Adult Smokers: A Multinational, 24-Week, Randomized, Double-Blind, Placebo-Controlled Study

Chris T. Bolliger, MD, PhD[1]; Jaqueline S. Issa, MD, PhD[2]; Rodolfo Posadas-Valay, MD[3]; Tarek Safwat, MD, FCCP[4]; Paula Abreu, DR.PH[5]; Eurico A. Correia, MD, MSc[6]; Peter W. Park, PhD[5]; and Pravin Chopra, MD[5]

[1]Respiratory Research Unit, Faculty of Health Sciences, University of Stellenbosch, Cape Town, South Africa; [2]Heart Institute, University of São Paulo, São Paulo, Brazil; [3]Hospital Universitario UANL, Centro de Prevención y Rehabilitación de Enfermedades Pulmonares Crónicas, Monterrey, Mexico; [4]Department of Chest Medicine, Ain Shams University, Cairo, Egypt; [5]Pfizer Inc, New York, New York; and [6]Pfizer Inc, São Paulo, Brazil

ABSTRACT

Background: Prevalence rates of smoking are rising in developing countries. Previous trials evaluating the efficacy and tolerability of the smoking-cessation medication varenicline have used largely participants of Caucasian origin.

Objective: This study was conducted to evaluate the efficacy and tolerability of varenicline in populations of participants from Latin America, Africa, and the Middle East to investigate potential differences in the therapeutic response to varenicline.

Methods: This multinational, randomized, double-blind, placebo-controlled trial was conducted at 42 centers in 11 countries (Latin America: Brazil, Colombia, Costa Rica, Mexico, and Venezuela; Africa: Egypt and South Africa; Middle East: Jordan, Lebanon, Saudi Arabia, and the United Arab Emirates). Participants were male and female smokers aged 18 to 75 years who were motivated to stop smoking; smoked ≥10 cigarettes/d, with no cumulative period of abstinence >3 months in the previous year; and who had no serious or unstable disease within the previous 6 months. Subjects were randomized in a 2:1 ratio to receive varenicline 1 mg or placebo, BID for 12 weeks, with a 12-week nontreatment follow-up. Brief smoking-cessation counseling was provided. The main outcome measures were carbon monoxide–confirmed continuous abstinence rate (CAR) at weeks 9 to 12 and weeks 9 to 24. Adverse events (AEs) were recorded for tolerability assessment.

Results: Overall, 588 subjects (varenicline, 390; placebo, 198) were randomized and treated. The mean (SD) ages of subjects in the varenicline and placebo groups were 43.1 (10.8) and 43.9 (10.8) years, respectively; 57.7% and 65.7% were male; and the mean (SD) weights were 75.0 (16.0) and 76.7 (16.3) kg (range, 40.0–130.0 and 45.6–126.0 kg). CAR at weeks 9 to 12 was significantly higher with varenicline than with placebo (53.59% vs 18.69%; odds ratio [OR] = 5.76; 95% CI, 3.74–8.88; $P < 0.0001$), and this rate was maintained during weeks 9 to 24 (39.74% vs 13.13%; OR = 4.78; 95% CI, 2.97–7.68; $P < 0.0001$). Nausea, headache, and insomnia were the most commonly reported AEs with varenicline and were reported numerically more frequently in the varenicline group compared with the placebo group. Serious AEs (SAEs) were reported in 2.8% of varenicline recipients compared with 1.0% in the placebo group, with 6 subjects reporting psychiatric SAEs compared with none in the placebo group.

Conclusion: Based on these data, varenicline was apparently efficacious and generally well tolerated as a smoking-cessation aid in smokers from selected sites in Latin America, Africa, and the Middle East. ClinicalTrials.gov identifier: NCT00594204. (*Clin Ther.* 2011;33:465–477) © 2011 Published by Elsevier HS Journals, Inc.

Key words: continuous abstinence rate, randomized trial, smoking cessation, varenicline.

INTRODUCTION

Smoking remains an important preventable cause of disease, and the estimated disease burden attributable

Table I. Prevalence of tobacco use and dates of treatment availability in selected countries.

Region/Country	Daily Smoking Prevalence, %			Date of Drug Availability		
	Men	Women	All	Varenicline	Bupropion	NRT
Latin America						
Venezuela	35.9	21.4	23.0*	May 2008	2000	1978
Costa Rica	29.0	9.7	6.0*	October 2007	1990	1978
Colombia	26.8	11.3	N/A	June 2007	1989	1978
Brazil	21.6	13.0	17.2†	August 2007	1997	1978
Mexico	12.9	4.7	18.5‡	December 2006	1989	1978
Africa						
Egypt	45.4	12.1	14.0*	June 2009	N/A	N/A
South Africa	23.2	7.7	16.0*	N/A	2003	1998
Middle East						
Jordan	50.5	8.3	36.0*	June 2008	N/A	2004
Lebanon	42.3	30.6	17.0*	June 2008	2003	2007
United Arab Emirates	17.3	1.3	8.0*	September 2007	2003	1998
Saudi Arabia	14.4	4.9	7.0*	August 2008	N/A	Available

NRT = nicotine-replacement therapy; N/A = treatment not available.
*Data from reference.[7]
†Data from reference.[8]
‡Data from reference.[9]

to smoking is >6 million premature deaths each year worldwide.[1] If current trends continue, the estimated deaths from tobacco during the 21st century will be 1 billion.[2] Smokers trying to quit frequently fail due to the addictive effect of nicotine. Pharmaceutical aids have been used successfully to help smokers quit; for example, nicotine-replacement therapy (NRT) has been found to increase the rate of abstinence by 50% to 70% compared with placebo.[3] Currently, 3 compounds are considered first-line therapies: NRT in various formulations; the antidepressant bupropion; and, more recently, varenicline, an $\alpha4\beta2$ nicotinic acetylcholine receptor partial antagonist.[4] Based on data from various published reports in the 2008 US Clinical Practice Guideline,[4] varenicline seems to be associated with higher abstinence rates than NRT[5] or bupropion.[6] However, these reports came from studies mainly conducted in the United States, Europe, and Asia.

Based on a MEDLINE search of studies published through 2008, no clinical trials of varenicline had been conducted in Latin America, Africa, or the Middle East. Nicotine use varies within these regions (Table I),[7–10] and while smoking rates are declining in the developed world, they are still rising in developing countries.[2]

Varenicline may have benefits in smokers in these countries with often-limited access to smoking-cessation interventions. While results from pivotal Phase III clinical trials are sufficient for many national health agencies to render a decision on the approval of a medication, clinical data from local patients are useful for assisting physicians in making individual treatment decisions. It is therefore important to determine the efficacy and tolerability of varenicline in smokers in unstudied populations. The aim of the present study was to evaluate the efficacy and tolerability of varenicline as an aid for smoking cessation in populations of cigarette smokers in Latin America, Africa, and the Middle East.

PARTICIPANTS AND METHODS
Study Design

This multinational, 24-week, randomized, double-blind, placebo-controlled efficacy and tolerability trial of varenicline was conducted from April 10, 2008, to August 17, 2009, at sites in Latin America (Brazil [7

Table II. Number of study sites and participants, by country.

Region/Country	Sites (N = 42)	Participants (N = 588)
Latin America		
Brazil	7	96
Venezuela	4	56
Mexico	3	100
Colombia	2	28
Costa Rica	1	21
Africa		
South Africa	13	130
Egypt	1	50
Middle East		
United Arab Emirates	6	60
Lebanon	2	26
Saudi Arabia	2	11
Jordan	1	10

sites], Venezuela [4], Mexico [3], Colombia [2], and Costa Rica [1]); Africa (South Africa [13] and Egypt [1]); and the Middle East (United Arab Emirates [6], Lebanon [2], Saudi Arabia [2], and Jordan [1]) (Table II). The investigative sites were smoking cessation clinics, medical centers, and hospitals.

The primary objective of this study was to evaluate the efficacy of 12 weeks of varenicline treatment (1 week of dose titration [0.5 mg once daily for 3 days followed by 0.5 mg BID for 4 days] followed by 11 weeks of varenicline 1 mg BID) compared with placebo for smoking cessation. Secondary objectives were to compare abstinence from cigarette smoking in the 12-week nontreatment follow-up period, and to evaluate the tolerability of varenicline.

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki,[11] was approved by the institutional review boards and independent ethics committees at each of the study sites, and was conducted in compliance with the standards on good clinical practice developed by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).[12] All of the participants provided

written informed consent before any study procedures were conducted or study medication was administered.

Participants

Eligible participants were male and female smokers aged 18 to 75 years, with a body mass index of 15 to 38 kg/m^2 (and a weight of at least 45.5 kg), who were motivated to stop smoking and had smoked a mean of ≥10 cigarettes/d during the previous 12 months and during the month before the screening visit, with no cumulative period of abstinence >3 months in the previous 12 months. Women of childbearing potential were included provided that they were not pregnant or breastfeeding and that they had agreed to practice an effective method of contraception through to at least 30 days after the administration of the last dose of study medication.

Smokers with serious or unstable disease within the 6 months before study entry (including cardiovascular disease, cerebrovascular disorders, and neurologic disorders) were not eligible for participation. Other exclusion criteria included a diagnosis of, or treatment for, depression during the previous 12 months; a history of or current psychosis, panic disorder, or bipolar disorder; severe chronic obstructive pulmonary disease; uncontrolled hypertension or systolic blood pressure (BP) >150 mm Hg or diastolic BP >95 mm Hg at the screening or baseline visit; a clinically significant endocrine disorder or gastrointestinal disease; clinically significant hepatic or renal impairment or other clinically significant laboratory abnormality; a history of a cancer (excluding basal cell or squamous cell carcinoma); a history of a clinically significant allergic reaction to a medication; a history of drug (with the exception of nicotine) or alcohol abuse or dependence within the previous 12 months; use of NRT, bupropion, clonidine, or nortriptyline within the previous 6 months; and/or participation in another study of an experimental drug for smoking cessation within the previous 12 months, or treatment with any medications that might interfere with the outcome of the trial.

Screening

The screening visit took place 3 to 14 days before the baseline visit (week 0). Data on demography, medical history, physical examination, vital signs (temperature, BP, heart rate, and respiratory rate), weight and height, ECG, pregnancy, biochemistry, hematology, and urinalysis were obtained. Pregnancy tests were

conducted by qualitative determination of serum or urine chorionic gonadotropin in women of childbearing potential at a local laboratory within 24 hours before study entry. Biochemistry testing included sodium, potassium, chloride, bicarbonate, blood urea nitrogen or serum urea, creatinine, glucose, calcium, inorganic phosphorus, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, alkaline phosphatase, total bilirubin, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, albumin, and total protein. Hematology testing included absolute blood cell counts with differential, including neutrophils, bands, lymphocytes, monocytes, eosinophils, and basophils; and hemoglobin, hematocrit, and platelet count. Urinalysis assessments were conducted using a dipstick and included specific gravity, pH, glucose, ketones, protein, hemoglobin, urobilinogen, eosinophils, urine bilirubin, nitrate, and leukocyte esterase. Samples for pregnancy, biochemistry, hematology, and urinalysis were sent to a local laboratory for analysis. A smoking history was also obtained, and eligible participants completed the Fagerström Test for Nicotine Dependence (FTND)[13] to determine the extent of nicotine dependence. The FTND is a 6-item test that scores nicotine dependence on a scale of 0 to 10, with higher scores reflecting greater nicotine dependence.

Interventions

Using a block randomization within each site, eligible participants were randomly assigned in a 2:1 ratio to receive varenicline or placebo. Active drug and placebo (provided as matching tablets) were orally administered with water. Identification numbers and study treatments were assigned to participants at the screening visit using a Web-based or telephone call-in drug-management system directed by the sponsor. All of the study personnel and participants were blinded to treatment assignment until the end of the nontreatment follow-up phase. All study medications and procedures were provided to participants free of charge.

Study treatment was dispensed at the baseline clinic visit (randomization), and participants were given *You Can Quit Smoking*,[14] an educational booklet on smoking cessation available in English, Spanish, Portuguese, and Arabic. Participants also received brief 1-on-1 smoking-cessation counseling (up to 10 minutes) in accordance with the Preventive Services Task Force guideline,[15] which was offered to participants at each subsequent visit (clinic and telephone) during the treat-

ment and follow-up phases. Participants were assigned a target quit date (TQD) (defined as the day on which the participant agreed to initiate smoking abstinence), which coincided with the first scheduled treatment visit (week 1). Each participant was contacted by telephone and reminded of his or her study participation and received brief counseling 3 days after the TQD. Participants returned for clinic visits at weeks 2, 3, 4, 6, 8, 10, and 12 during the treatment phase and at weeks 13, 16, 20, and 24 during the nontreatment follow-up period. Assessments by telephone were conducted at weeks 14, 18, and 22.

Vitals signs and weight were measured at each clinic visit throughout the study period. Physical examination, ECG, blood chemistry, hematology, and urinalyses were repeated at week 12 or at early termination. Use of nicotine-containing products, changes in concurrent medications, and reports of adverse events (AEs) were assessed at each study visit. Those who discontinued study treatment prematurely were encouraged to participate in the remaining study visits through the nontreatment follow-up period.

Smoking Status

Smoking status was assessed using the nicotine-use inventory (NUI) (a self-completion questionnaire documenting the use of cigarettes and other nicotine-containing products, designed for, and implemented in, previous varenicline studies[6,16]), which was administered at baseline and at all subsequent study visits. Self-reported smoking abstinence was confirmed by end-expiratory exhaled carbon monoxide (CO) ≤10 ppm at each clinic visit using a breath CO monitor (Micro IV Smokerlyzer, Bedfont Scientific Ltd, Rochester, United Kingdom), which is considered an appropriate measure for biochemical verification and has been used in previously published clinical trials of smoking-cessation treatments.[17,18] Participants with CO measurements >10 ppm were considered nonabstinent during the period associated with the measurement.

Adverse Events

All reported or observed AEs were documented on case-report forms, which were provided, collected, and monitored by the sponsor and followed up from the administration of the first dose of study treatment until resolution or the end of the study. AEs were reported descriptively using the coding from the Medical Dictionary for Regulatory Activities (MedDRA) version

12. All AEs were tabulated using the Treatment Emergent Signs and Symptoms (TESS) algorithm. Descriptive statistics rather than inferential statistics were used to compare treatment arms with respect to AE data due to challenges of controlling Type I error in multiple comparisons.

Serious AEs (SAEs) and severe AEs were also documented on case-report forms and reported to the sponsor. The US Food and Drug Administration and ICH definition of an SAE was used in this trial. Thus, an AE was recorded as an SAE if it resulted in death, was life-threatening, required inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent/significant disability/incapacity, and/or led to congenital anomaly/birth defect. An AE was considered severe if it interfered significantly with subject's usual functioning.

Outcomes Measures
Primary End Point

The primary end point was the CO-confirmed 4-week continuous abstinence rate (CAR) for weeks 9 to 12, with *CAR* defined as the proportion of participants who maintained complete abstinence (not even a puff) from the use of cigarettes and other nicotine-containing products during this period. Smoking abstinence was assessed using the NUI and was verified using measurements of end-expiratory exhaled CO.

Secondary End Points

Secondary end points included the CO-confirmed CAR during weeks 9 to 24; 7-day point prevalence of nonsmoking at weeks 12 and 24; and the incidence rate of AEs, premature discontinuations during the study, and clinically significant changes in vital signs. The *7-day point prevalence at weeks 12 and 24* was defined as the proportion of participants who had not used cigarettes or any other nicotine-containing product during the 7 days before the assessment.

Statistical Analysis

All of the primary and secondary end points were analyzed in the *full-analysis population,* defined as participants who took at least 1 dose, including a partial dose, of study medication.

All statistical testing was 2-sided with a Type I error rate of 0.05. A step-down procedure was used in the analysis of the primary and key secondary end points to preserve the Type I error rate of 0.05. No adjustments were made for the analysis of multiple other secondary end points. The hierarchy of comparisons between varenicline and placebo was as follows: (1) the 4-week CAR for weeks 9 to 12 and (2) the CAR for weeks 9 to 24. SAS version 8.2 (SAS Institute Inc, Cary, North Carolina) was used for all analyses.

Abstinence end points were analyzed as binary data using the logistic regression model, which included the main effects of treatment group and investigative country as independent variables. Treatment-by-center interaction was investigated; however, the reported *P* values were based on the main-effects model. All significance tests were 2-tailed using a significance level of 0.05.

It was important to power this study for the primary (CAR at weeks 9–12) and key secondary (CAR at weeks 9–24) end points. To achieve 90% power to detect significant differences in the secondary end point in a 2-group, continuity-corrected χ^2 test with $\alpha = 0.05$ for the comparison of varenicline with placebo, the calculated sample size was a minimum of 270 participants (180 in the varenicline group and 90 in the placebo group). The actual sample size of 588 used in this study provided ≥95% power to detect significant differences in the primary end point. Estimates for expected varenicline and placebo CAR at weeks 9 to 12 and weeks 9 to 24 were based on results from a similarly designed previously published study[19] but are more conservative.

Only participants who attended clinic visits and met both the NUI and CO criteria were considered abstinent. Participants who discontinued from the study and were lost to follow-up for subsequent visits were assumed to be smokers for the remainder of the study. In binary responder assessments, subjects who discontinued were represented in the denominator but not in the numerator, regardless of smoking status at the time of discontinuation, which might be considered a worst-case-carried-forward analysis and represents a conservative approach to the imputation of missing data.

RESULTS
Participant Disposition

Of the 689 individuals who were screened, 593 (86.1%) were randomized (Figure 1). Overall, 588 participants received at least 1 dose of study treatment (varenicline, 390; placebo, 198) and were included in the full-analysis population. Of the 5 participants who
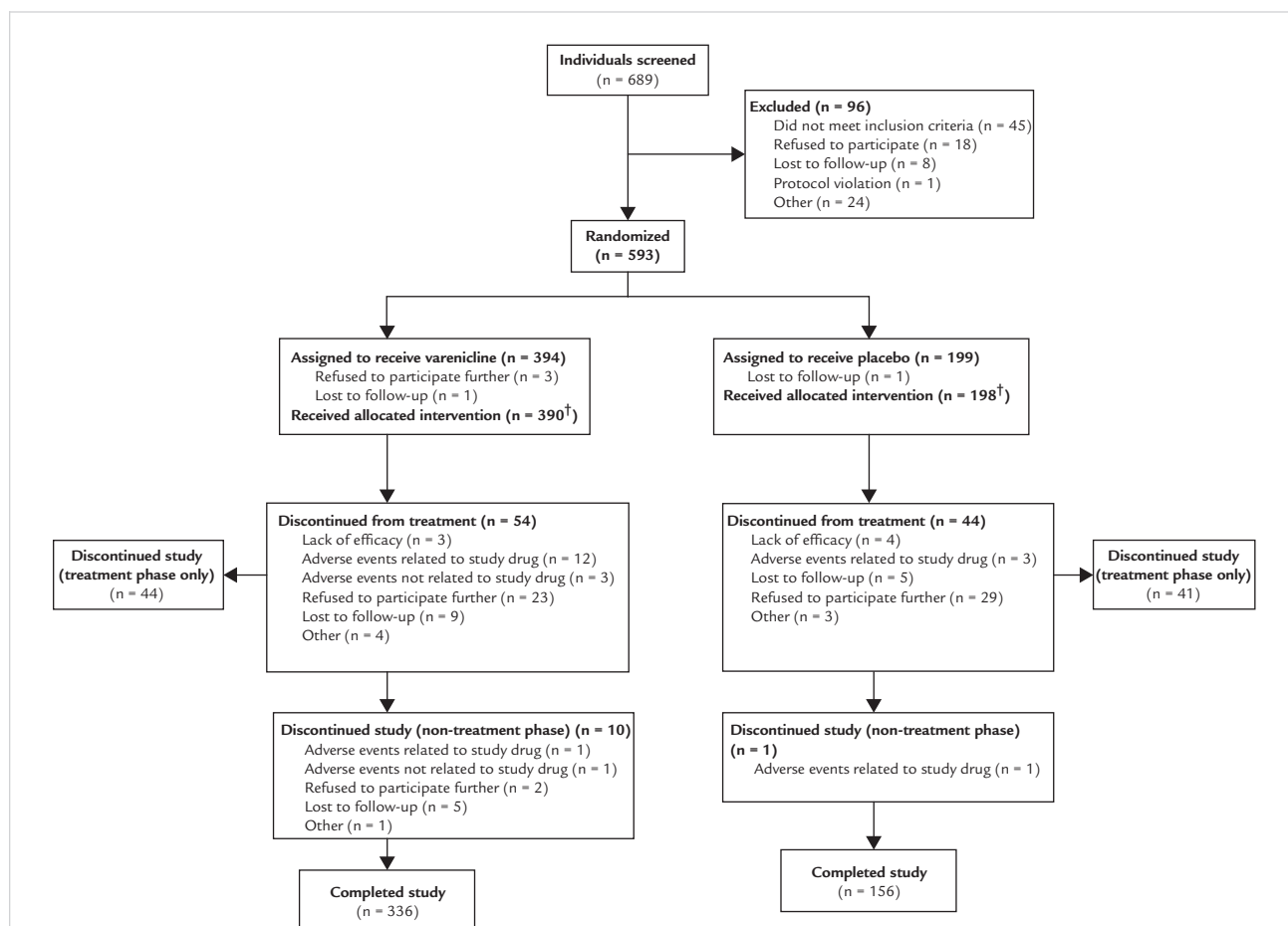
Figure 1. Participant disposition. *Included participants who did not meet the inclusion criteria, had 1 or more protocol violations, or "other." †All participants who received at least 1 dose or partial dose of study medication were included in the efficacy and tolerability analyses.

were randomized but did not receive study treatment, 3 were no longer willing to participate (all in the varenicline group) and 2 were lost to follow-up (varenicline, 1; placebo, 1). A total of 336 of 394 (85.3%) participants assigned to receive varenicline and 156 of 199 (78.4%) assigned to receive placebo completed the study. Overall, the study-completion rates at week 24 were 336 of 390 (86.2%) in the varenicline group and 156 of 198 (78.8%) in the placebo group. Overall, 54 (13.8%) participants in the verenicline and 42 (21.2%) participants in the placebo arm discontinued the study.

Participant enrollment per region was as follows: Latin America, 301 (51.2%); Africa, 180 (30.6%); and the Middle East, 107 (18.2%) (Table II). The demographic characteristics were statistically similar between the 2 treatment groups (Table III). The mean

ages of the participants were 43.1 years (range, 18–69 years) and 43.9 years (range, 20–71 years) in the varenicline and placebo groups, respectively. The majority of the participants in the 2 groups were male (225 [57.7%] and 130 [65.7%]). The mean weights of participants in the varenicline and placebo groups were 75.0 and 76.7 kg, respectively. There were no statistically significant differences in smoking history between the 2 treatment groups. The mean numbers of cigarettes smoked per day over the month before the study were 23.8 and 23.7 in the varenicline and placebo groups. The mean number of years that the participants smoked were 25.0 and 26.8, and the mean ages at which the participants started smoking were 17.7 and 16.7 years. The varenicline group had a mean (SD) FTND score of 6.0 (2.2), and the placebo group had a mean score of 6.1 (2.0) of a possible total score of 10.

Table III. Baseline demographic and clinical characteristics of the study population.*

Characteristic	Varenicline (n = 390)	Placebo (n = 198)
Age, y		
Mean (SD)	43.1 (10.8)	43.9 (10.8)
Range	18–69	20–71
Sex, no. (%)		
Male	225 (57.7)	130 (65.7)
Female	165 (42.3)	68 (34.3)
Race, no. (%)[†]		
White	118 (30.3)	62 (31.3)
Black	26 (6.7)	15 (7.6)
Asian	26 (6.7)	9 (4.5)
Other[‡]	220 (56.4)	112 (56.6)
Weight, kg		
Mean (SD)	75.0 (16.0)	76.7 (16.3)
Range	40.0–130.0	45.6–126.0
Height, cm		
Mean (SD)	168.2 (9.3)	169.4 (9.6)
Range	134.0–193.0	143.0–203.0
Body mass index, kg/m^2		
Mean (SD)	26.4 (4.8)	26.6 (4.4)
Range	16.8–43.6	17.0–38.6
Risk factors		
Age started smoking, y		
Mean	17.7	16.7
Range	9.0–41.0	8.0–37.0
Years of smoking, y		
Mean	25.0	26.8
Range	1.0–57.0	6.0–58.0
Cigarettes/d over previous month		
Mean	23.8	23.7
Range	10.0–90.0	10.0–80.0
Years smoking at this rate		
Mean	12.3	13.8
Range	0.1–57.0	0.0–50.0
Lifetime serious quit attempts,[§] no. (%) of participants		
0	212 (54.4)	109 (55.1)
1	99 (25.4)	54 (27.3)
2	27 (6.9)	13 (6.6)
≥3	52 (13.3)	22 (11.1)
Fagerström score[13] for nicotine dependence, mean (SD)[‖]	6.0 (2.2)	6.1 (2.0)

*No significant between-group differences were found.
[†]Percentages may not total 100 due to rounding.
[‡]Included Arab, Caucasian, Hispanic, and mixed races.
[§]Number of quit attempts and/or number of quit methods used.
[‖]Range: 0 = no nicotine dependence to 10 = highest nicotine dependence.

There were small but nonsignificant differences in smoking history between the 3 geographic regions, with the mean number of cigarettes/d smoked over the previous month being highest in the Middle East (27.4 and 29.5 in the active-treatment group vs placebo; Africa, 23.7 vs 23.4; Latin America, 22.7 vs 21.7), and the mean FTND scores being highest in the African region (6.7 vs 6.4; Middle East, 6.3 vs 6.0; Latin America, 5.5 vs 5.9).

Concurrent use of medication was statistically similar between the 2 treatment groups. Approximately 67.4% of the participants in the varenicline group and 65.7% of participants in the placebo group used some form of concurrent drug treatment, the most common of which were analgesics (24.1% and 22.2% in the varenicline and placebo groups, respectively).

Efficacy
Continuous Abstinence

The CO-confirmed CAR at weeks 9 to 12 was significantly higher with varenicline (53.59%) compared with placebo (18.69%) (odds ratio [OR] = 5.76; 95% CI, 3.74–8.88; $P < 0.0001$) (Figure 2). CAR at weeks 9 to 24 was significantly higher with varenicline compared with placebo (39.74% vs 13.13%; OR = 4.78; 95% CI, 2.97–7.68; $P < 0.0001$). Because the 2 treatment groups received identical smoking-cessation counseling (10-minute duration), any effect of counseling on efficacy outcomes would be expected to have been similar between the 2 groups. Treatment-by-center interactions were found to be nonsignificant. Exploratory logistic regression analyses showed no statistically significant treatment differences based on participant age, sex, or FTND score.

Point Prevalences of Abstinence Rates

The 7-day point prevalences of abstinence rates were significantly higher with varenicline compared with placebo at the end of treatment (week 12; 56.4% vs 22.7% [$P < 0.0001$]) and at the end of follow-up (week 24; 47.4% vs 19.2% [$P < 0.0001$]). At all assessments, the 7-day point prevalences of abstinence rates were significantly higher with varenicline compared with placebo (Figure 3).

Tolerability

All-causality, treatment-emergent AEs were reported in 262 (67.2%) participants in the varenicline group and 108 (54.5%) participants in the placebo group (Table IV). The treatment-emergent AEs most
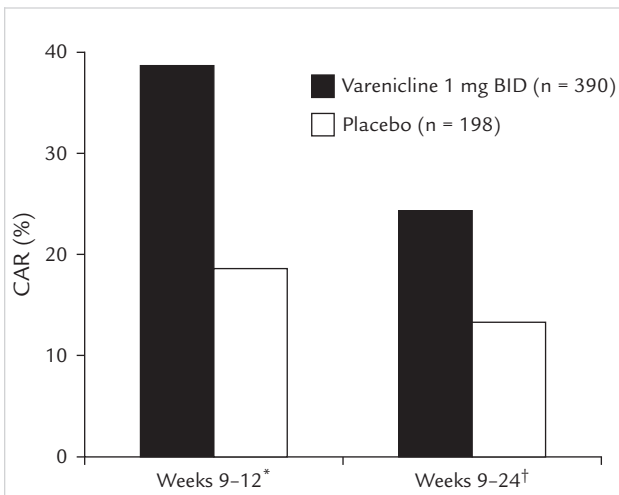
Figure 2. Carbon monoxide (CO)-confirmed smoking continuous abstinence rates (CAR) at weeks 9 to 12 and weeks 9 to 24. At each visit from week 9 through the given time point, these participants reported no use of cigarettes or other nicotine-containing products since the previous study visit (on the nicotine-use inventory [a self-completion questionnaire documenting the use of cigarettes and other nicotine-containing products, designed for, and implemented in, previous varenicline studies[6,16]]) and did not have CO >10 ppm (when assessed at a clinic visit). *Odds ratio (OR) = 5.76; 95% CI, 3.74–8.88; $P < 0.0001$; †OR = 4.78; 95% CI, 2.97–7.68; $P < 0.0001$ (ORs and P values were obtained from logistic regression modeling, including the main effects of treatment and country).

frequently reported (5% or more of the participants) with varenicline compared with placebo are shown in Table V. Nausea was the most commonly reported AE in the varenicline group (103 [26.4%]), followed by headache (64 [16.4%]), insomnia (50 [12.8%]), and constipation (23 [5.9%]).

Severe AEs were reported in 32 participants (8.2%) in the varenicline group and in 10 participants (5.1%) in the placebo group (Table IV). Overall, AEs that resulted in permanent study discontinuations were reported in 19 participants, with a 4.1% incidence of discontinuations in varenicline-treated participants (n = 16) versus 1.5% in placebo-treated participants (n = 3).

All-causality, treatment-emergent psychiatric AEs included anxiety disorders (23 [5.9%] in the varenicline group vs 17 [8.6%] in the placebo group); depressed mood disorders (12 [3.1%] in the varenicline group vs 7 [3.5%] in the placebo group); and suicidal and self-injurious behaviors (2 [0.5%] in the varenicline group vs 0 in the placebo group) (Table VI). There were 2 cases of suicidal ideation in the varenicline group (0.5%), 1 of which was considered to be treatment related. In addition, a 52-year-old male participant reported a suicide attempt during the nontreatment phase, at 49 days after the administration of last dose of study drug; the event was considered unrelated to the study drug. Overall, 4 psychiatric AEs in 3 participants who received varenicline were reported as SAEs (suicidal ideation and depressed mood, suicidal ideation, and panic attack).

Across the 2 treatment groups, 13 participants (varenicline, 11 [2.8%]; placebo, 2 [1.0%]) reported 20 SAEs during the 12 weeks of treatment or within 30 days of the administration of the last dose of study medication (Table IV). In the varenicline group, SAEs were (by preferred term) abortion; hypersensitivity; overdose; bronchitis and asthma; nasal septum deviation; suicidal ideation and depressed mood; suicidal ideation; tachycardia, bradycardia, and dyspnea; panic attack; injury; and appendicitis.
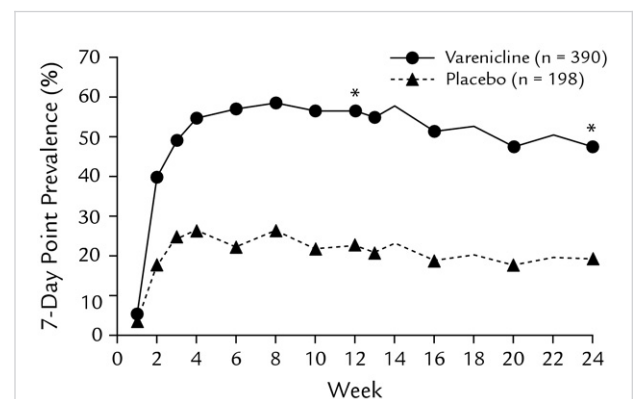

Figure 3. Seven-day point prevalences of abstinence. Abstinence from any nicotine-containing product in the previous 7 days was carbon monoxide-confirmed at clinic visits (solid symbols). Assessments by telephone were conducted at weeks 14, 18, and 22 (open symbols). *$P < 0.0001$ versus placebo.

Table IV. Adverse events (AEs). Data are number (%) of participants.*

Parameter	Varenicline (n = 390)	Placebo (n = 198)
Any AE	262 (67.2)	108 (54.5)
Serious AE[†]	11 (2.8)	2 (1.0)
Severe AE[‡]	32 (8.2)	10 (5.1)
Treatment discontinuation		
All-causality AE	16 (4.1)	3 (1.5)
Treatment-related AE	12 (3.1)	3 (1.5)

*Includes data up to 30 days after the administration of the last dose of study drug. Includes all AEs reported in the *Medical Dictionary for Regulatory Activities System Organ Class of Psychiatric Disorders*, Version 12.
[†]Defined as any AE that resulted in death, was life-threatening, required inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent/significant disability/incapacity, and/or led to congenital anomaly/birth defect.
[‡]Defined as any AE that significantly interfered with the subject's usual functioning.

In the placebo group, SAEs were thyroid neoplasm; and peritonitis, appendicitis, and diverticulitis. None of the participants died during the study period.

The overdose in the varenicline group was reported in a 51-year-old man with a history of cervical spondylosis and depression, who was experiencing a severe frontal headache. In an attempt to treat the headache, the subject took 14 carbamazepine and 2 paracetamol/codeine phosphate tablets on the same day. He was found semiconscious, was admitted to a hospital, and was diagnosed as having had a drug overdose. The subject was given IV fluids but no medication was administered. He was discharged in stable condition and remained in the study. The event was considered by the investigator as unrelated to study drug.

An abortion was reported in a 32-year-old woman in the varenicline group who had discovered that she was pregnant ~1 month into the study, immediately discontinued treatment, and 9 days after discontinuation experienced bleeding and a confirmed abortion at the hospital. The investigator concluded that a contributory role of the study medication could not be excluded.

A spontaneous abortion was reported in a 25-year-old woman in the varenicline group who had become pregnant ~1 month into the study, discontinued treatment, and 2 months after discontinuation experienced an abortion; the investigator did not consider the event related to the study drug.

DISCUSSION

In this randomized, placebo-controlled study in smokers from Latin America, Africa, and the Middle East, varenicline was apparently efficacious in achieving smoking cessation, and was considered generally well tolerated. In this study, varenicline was associated with a significantly higher CAR for the last 4 weeks of treatment (CAR weeks 9–12; 53.59% vs 18.69%; OR = 5.76; 95% CI, 3.74–8.88; $P < 0.0001$) compared with placebo. Importantly, varenicline also was associated with a significantly higher CAR at weeks 9 to 24 (39.74% vs 13.13%; OR = 4.78; 95% CI, 2.97–7.68; $P < 0.0001$) compared with placebo. The 7-day point prevalences of abstinence at the end of treatment (week 12) and at the end of follow-up (week 24) were also significantly higher with varenicline compared with placebo.

Table V. Most frequently reported treatment-emergent adverse events (AE) (all-causality). Data are number (%) of participants.*

AE	Varenicline (n = 390)	Placebo (n = 198)
Gastrointestinal disorders	151 (38.7)	43 (21.7)
Nausea	103 (26.4)	16 (8.1)
Constipation	23 (5.9)	10 (5.1)
Nervous system disorders	92 (23.6)	41 (20.7)
Headache	64 (16.4)	24 (12.1)
Psychiatric disorders	90 (23.1)	30 (15.2)
Insomnia	50 (12.8)	13 (6.6)
Anxiety	16 (4.1)	15 (7.6)
Infections and infestations	76 (19.5)	39 (19.7)
Influenza	14 (3.6)	12 (6.1)

*All observed or self-reported AEs that occurred in ≥5% of participants. Includes data up to 30 days after the administration of the last dose of study drug. Includes all AEs reported in the *Medical Dictionary for Regulatory Activities System Organ Class of Psychiatric Disorders*, Version 12.

Table VI. Treatment-emergent psychiatric adverse events (AE) (all-causality).*

AE	Varenicline (n = 390)	Placebo (n = 198)
Sleep disorders or disturbances		
Abnormal dreams, insomnia, nightmare, sleep disorder	66 (16.9)	15 (7.6)
Anxiety disorders or symptoms		
Agitation, anxiety, nervousness, obsessive thoughts, stress	23 (5.9)	17 (8.6)
Depressed mood disorders or disturbances		
Depression, depressed mood, depressive symptom, dysthymia	12 (3.1)	7 (3.5)
Other mood disorders or disturbances		
Anger, flat affect, mood altered	5 (1.3)	4 (2.0)
Suicidal and self-injurious behaviors		
Suicidal ideation	2 (0.5)	0
Sexual dysfunction and fertility disorders		
Erectile dysfunction	3 (0.8)	1 (0.5)
Disturbance in attention	2 (0.5)	1 (0.5)
Disturbances in behavior		
Aggression	1 (0.3)	0

*Includes data up to 30 days after the administration of the last dose of study drug. Includes all AEs reported in the Medical Dictionary for Regulatory Activities System Organ Class of Psychiatric Disorders, version 12. Each row represents a higher-level group term, which is a combination of the individual symptom terms listed below the group term.

Comparison With Other Studies

The OR for CAR at weeks 9 to 12 in this study (OR = 5.76; 95% CI, 3.74–8.88; $P < 0.0001$) was higher than those observed in previously published clinical trials that measured the CAR of varenicline versus placebo in generally healthy smokers.[6,16,19,20] In 2 early Phase III studies in white subjects, CAR at weeks 9 to 12 was reported to be 43.9% with varenicline versus 17.6% with placebo (OR = 3.85; 95% CI, 2.7–5.5; $P < 0.001$)[16] and 44.0% versus 17.7%, respectively (OR = 3.85; 95% CI, 2.7–5.5; $P < 0.001$).[6] More importantly, the OR for CAR at weeks 9 to 24 compared favorably with those from all of the previously published varenicline studies found in the MEDLINE search, including 2 studies in nonwhite populations.[19,20] The CIs of the ORs, however, overlapped. Tsai et al[19] reported that the CAR at weeks 9 to 24 with varenicline versus placebo was 46.8% versus 21.8% (OR = 3.38; 95% CI, 1.9–5.99; $P < 0.001$) in a cohort of Korean and Taiwanese smokers. Although the abstinence rate in the group receiving the active

drug was higher than that in the present study, there was a high abstinence rate in the placebo group as well, which negatively affected the OR. In another study, conducted by Wang et al[20] in a population from China, Singapore, and Thailand, the abstinence rates were 38.2% and 25.0% with active treatment and placebo, respectively (OR = 1.92; 95% CI, 1.18–3.13; $P = 0.0080$). Higher placebo effects were observed in these 2 studies compared with that in the present study.

In the present study, the likelihood of quitting smoking with varenicline was higher compared with those in 2 previously reported meta-analyses.[4,21] The first, published by the US Department of Health and Human Services, Public Health Service, reported an estimated pooled OR of 3.1 (95% CI, 2.5–3.8) for studies comparing the effects of varenicline 2 mg/d with those of placebo at 6 months after quit date compared with an OR = 4.78 at weeks 9 to 24 in the present study.[4] In a Cochrane systematic review of 6 randomized, controlled trials investigating nicotine receptor partial agonists, varenicline was reported to be associated with a significant (~3-fold)

increase in CAR at 12 months versus placebo (pooled OR = 3.22; 95% CI, 2.43–4.27).[21] However, the longer duration of the trials included in the Cochrane meta-analysis makes a direct comparison with the results from the present 24-week study difficult.

Meaning of the Study

The apparently greater likelihood of quitting smoking with varenicline compared with placebo observed in the present study might be attributable to the limited access to smoking-cessation interventions generally available in Latin American, African, and Middle Eastern countries. Of note is the low percentage of smokers with previous quit attempts in this study—more than half of participants had made no serious prior quit attempt (54.4% in the varenicline arm; 55.1% in the placebo arm). The FTND scores in these participants were high, reflecting a high degree of nicotine dependence.

The results from this study suggest that varenicline was well tolerated, with a safety profile similar to those in observations from previously published studies. As in previous studies, the most frequently reported AEs were nausea, headache, and insomnia, reported at frequencies comparable to those from previously published varenicline trials.[6,16] Anxiety was reported in fewer participants on active treatment compared with placebo (4.1% vs 7.6%), although this difference has not been tested for statistical inferences. Overall, this study further adds to the growing database of clinical trials the results of which suggest that varenicline is well tolerated.

There have been postmarketing reports of serious neuropsychiatric symptoms in smokers taking varenicline, including suicidal thoughts and attempts and completed suicides. In 2009, varenicline received a "boxed warning" regarding neuropsychiatric SAEs. In the United States, a nonprofit group called the Institute of Safe Medication Practices issued several reports regarding the safety of varenicline based on neuropsychiatric postmarketing reports and called for restrictions on its use.[22,23] A published review of varenicline tolerability by a Veterans Affairs Health System in the United States recommended that, based on the numerous reported AEs and published case studies, selective initiation of varenicline and close follow-up are warranted, especially in subjects with preexisting psychiatric illness.[24] Due to the potential for these types of events, continued medical research into the neuropsychiatric safety profile of varenicline is essential.

To understand the potential risk based on data from randomized clinical trials, Tonstad et al[25] conducted a systematic, quantitative review of 10 placebo-controlled trials in smokers with no current or recent psychiatric disorder. The study reported risk differences for psychiatric disorders <1.0% between the varenicline and placebo groups, with the exception of sleep disorders and disturbances, which were increased by 10% (95% CI, 7.9 to 12.3) in the varenicline group. The highest risk increase was 0.8% (95% CI, −0.06 to 1.67) for depressed mood disorders and disturbances in the varenicline group versus placebo. The rate of suicidal and self-injurious behaviors was 0.12% (95% CI, −0.27 to 0.04) higher in the placebo group compared with the active-treatment arm. The 10 studies used in that review were not designed to differentiate between abstinence and medication effects.

Strengths and Limitations of the Study

The results from this study suggest that varenicline is an effective smoking-cessation aid in participants from Latin American, African, and Middle Eastern countries. Results suggest consistency across the regions. Limitations of this study were the stringent participant exclusion criteria, which, while necessary for this study in these populations, limit the generalizability of the results across wider smoking populations. Race identity data were collected according to a self-reporting method by the participants and therefore the authors cannot make more specific conclusions on smoking and race or ethnicities. In addition, the participants were found to have wide ranges of weight and body mass index values at baseline, although the few participants with higher values were outliers. Consequently, caution should be used in interpreting these results across participants. Differences in varenicline experience were reported in lower-weight subjects in a previously published pharmacokinetic study.[26] The variability in health care access, and population demography and population characteristics, restrict a more definite extrapolation of the study results across regions and, more specifically, across countries.

Future Research

As this study was conducted at selected sites in Latin America, Africa, and the Middle East, which have large socioeconomic differences and widely varying smoking prevalence, it is interesting to compare the efficacy outcomes between regions. The results (not shown) seem to indicate that there are no relevant differences between the individual regions. However, the study was

limited in that it was powered only for an efficacy analysis, and therefore did not allow for statistical conclusions for a safety subanalysis. Looking at additional regional effects would be of interest in future studies.

CONCLUSION

Varenicline was efficacious as an aid for smoking cessation but was associated with a numerically larger number of AEs compared with placebo in these adult smokers from 11 countries in Latin America, Africa, and the Middle East.

REFERENCES

1. World Health Organization. The World Report 2002: reducing risks, promoting healthy life. http://www.who.int/whr/2002/en/whr02_en.pdf. Accessed March 30, 2010.

2. Wipfli H, Samet JM. Global economic and health benefits of tobacco control: part 1. *Clin Pharmacol Ther.* 2009;86:263–271.

3. Stead LF, Perera R, Bullen C, et al. Nicotine replacement therapy for smoking cessation. *Cochrane Database Syst Rev.* 2008:CD000146.

4. Fiore MC, Jaén CR, Baker TB, et al, for the US Dept of Health and Human Services, Public Health Service. Clinical practice guideline. Treating tobacco use and dependence: 2008 update. http://www.surgeongeneral.gov/tobacco/treating_tobacco_use08.pdf. Accessed March 30, 2010.

5. Stapleton JA, Watson L, Spirling LI, et al. Varenicline in the routine treatment of tobacco dependence: a pre-post comparison with nicotine replacement therapy and an evaluation in those with mental illness. *Addiction.* 2008;103: 146–154.

6. Gonzales D, Rennard SI, Nides M, et al, for the Varenicline Phase 3 Study Group. Varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, vs sustained-release bupropion and placebo for smoking cessation: a randomized controlled trial. *JAMA.* 2006;296:47–55.

7. World Health Organization. WHO report on the global tobacco epidemic, 2009: implementing smoke-free environments. http://whqlibdoc.who.int/publications/2009/9789241563918_eng_full.pdf. Accessed March 30, 2010.

8. Centers for Disease Control and Prevention. Global Adult Tobacco Survey (GATS): Fact Sheet: Brazil. http://www.cdc.gov/tobacco/global/gats/countries/amr/fact_sheets/brazil/. Accessed March 30, 2010.

9. Instituto Nacional de Salud Publica [National Institute of Public Health]. Encuesta Nacional de Adicciones [National Survey on Addictions], 2008. http://www.conadic.salud.gob.mx/pie/ena2008html. Accessed March 30, 2010.

10. Mackay J, Eriksen M, Shafey O. *The Tobacco Atlas.* 2nd ed. Atlanta, Ga: American Cancer Society; 2006.

11. World Medical Association. WMA Declaration of Helsinki—Ethical principles for medical research involving human subjects. http://www.wma.net/en/30publications/10policies/b3/index.html. Accessed March 30, 2010.

12. The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). The ICH Process for Harmonization of Guidelines. http://www.ich.org/about/process-of-harmonisation.html. Accessed March 30, 2010.

13. Heatherton TF, Kozlowski LT, Frecker RC, Fagerström KO. The Fagerström Test for Nicotine Dependence: a revision of the Fagerström Tolerance Questionnaire. Br J Addict. 1991;86:1119–1127.

14. US Dept of Health and Human Services, Public Health Service, Agency for Healthcare Research and Quality. You can quit smoking. Consumer guide. http://www.ahrq.gov/consumer/tobacco/quits.htm. Accessed March 30, 2010.

15. Preventive Services Task Force. Counseling to prevent tobacco use and tobacco-caused disease: recommendation statement. http://www.uspreventiveservicestaskforce.org/uspstf/uspstbac.htm. Accessed March 30, 2010.

16. Jorenby DE, Hays JT, Rigotti NA, et al, for the Varenicline Phase 3 Study Group. Efficacy of varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, vs placebo or sustained-release bupropion for smoking cessation: a randomized controlled trial [published correction appears in: JAMA. 2006;296:1355]. JAMA. 2006;296:56–63.

17. Gonzales DH, Nides MA, Ferry LH, et al. Bupropion SR as an aid to smoking cessation in smokers treated previously with bupropion: a randomized placebo-controlled study. Clin Pharmacol Ther. 2001;69:438–444.

18. Jorenby DE, Leischow SJ, Nides MA, et al. A controlled trial of sustained-release bupropion, a nicotine patch, or both for smoking cessation. N Engl J Med. 1999;340:685–691.

19. Tsai ST, Cho HJ, Cheng HS, et al. A randomized, placebo-controlled trial of varenicline, a selective alpha4beta2 nicotinic acetylcholine receptor partial agonist, as a new therapy for smoking cessation in Asian smokers. Clin Ther. 2007;29:1027–1039.

20. Wang C, Xiao D, Chan KP, et al. Varenicline for smoking cessation: a placebo-controlled, randomized study. Respirology. 2009;14:384–392.

21. Cahill K, Stead LF, Lancaster T. Nicotine receptor partial agonists for smoking cessation. Cochrane Database Syst Rev. 2011:CD006103.

22. Moore TJ, Glenmullen J, Furberg CD. Prescription drugs associated with reports of violence towards others. PLoS One. 2010;5:e15337.

23. Moore TJ, Glenmullen J, Furberg CD. Thoughts and acts of aggression/violence toward others reported in association with varenicline. Ann Pharmacother. 2010;44:1389–1394.

24. Purvis TL, Nelson LA, Mambourg SE. Varenicline use in patients with mental illness: an update of the evidence. Expert Opin Drug Saf. 2010;9:471–482.

25. Tonstad S, Davies S, Flammer M, et al. Psychiatric adverse events in randomized, double-blind, placebo-controlled clinical trials of varenicline: a pooled analysis. Drug Saf. 2010;33:289–301.

26. Faessel H, Ravva P, Williams K. Pharmacokinetics, safety, and tolerability of varenicline in healthy adolescent smokers: a multicenter, randomized, double-blind, placebo-controlled, parallel-group study. Clin Ther. 2009;31:177–189.

Address correspondence to: Chris T. Bolliger, MD, PhD, Respiratory Research Unit, Faculty of Health Sciences, University of Stellenbosch, Cape Town, 7505 South Africa. E-mail: ctb@sun.ac.za