Effect of Varenicline on Smoking Cessation Through Smoking Reduction: A Randomized Clinical Trial

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**IMPORTANCE** Some cigarette smokers may not be ready to quit immediately but may be willing to reduce cigarette consumption with the goal of quitting.

**OBJECTIVE** To determine the efficacy and safety of varenicline for increasing smoking abstinence rates through smoking reduction.

**DESIGN, SETTING, AND PARTICIPANTS** Randomized, double-blind, placebo-controlled, multinational clinical trial with a 24-week treatment period and 28-week follow-up conducted between July 2011 and July 2013 at 61 centers in 10 countries. The 1510 participants were cigarette smokers who were not willing or able to quit smoking within the next month but willing to reduce smoking and make a quit attempt within the next 3 months. Participants were recruited through advertising.

**INTERVENTIONS** Twenty-four weeks of varenicline titrated to 1 mg twice daily or placebo with a reduction target of 50% or more in number of cigarettes smoked by 4 weeks, 75% or more by 8 weeks, and a quit attempt by 12 weeks.

**MAIN OUTCOMES AND MEASURES** Primary efficacy endpoint was carbon monoxide–confirmed self-reported abstinence during weeks 15 through 24. Secondary outcomes were carbon monoxide–confirmed self-reported abstinence for weeks 21 through 24 and weeks 21 through 52.

**RESULTS** The varenicline group (n = 760) had significantly higher continuous abstinence rates during weeks 15 through 24 vs the placebo group (n = 750) (32.1% for the varenicline group vs 6.9% for the placebo group; risk difference (RD), 25.2% [95% CI, 21.4%-29.0%]; relative risk (RR), 4.6 [95% CI, 3.5-6.1]). The varenicline group had significantly higher continuous abstinence rates vs the placebo group during weeks 21 through 24 (37.8% for the varenicline group vs 12.5% for the placebo group; RD, 25.2% [95% CI, 21.1%-29.4%]; RR, 3.0 [95% CI, 2.4-3.7]) and weeks 21 through 52 (27.0% for the varenicline group vs 9.9% for the placebo group; RD, 17.1% [95% CI, 13.3%-20.9%]; RR, 2.7 [95% CI, 2.1-3.5]). Serious adverse events occurred in 3.7% of the varenicline group and 2.2% of the placebo group (P = .07).

**CONCLUSIONS AND RELEVANCE** Among cigarette smokers not willing or able to quit within the next month but willing to reduce cigarette consumption and make a quit attempt at 3 months, use of varenicline for 24 weeks compared with placebo significantly increased smoking cessation rates at the end of treatment, and also at 1 year. Varenicline offers a treatment option for smokers whose needs are not addressed by clinical guidelines recommending abrupt smoking cessation.

**TRIAL REGISTRATION** clinicaltrials.gov Identifier: NCT01370356


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Forty percent of cigarette smokers make an average of 2 quit attempts annually.1 In a telephone survey of 1000 current daily cigarette smokers, 44% reported a preference to quit through reduction in the number of cigarettes smoked, and 68% would consider using a medication to facilitate smoking reduction.2 However, US clinical practice guidelines3 recommend that smokers quit abruptly even though only 8% of smokers report being ready to quit in the next month.4 Developing effective interventions to achieve tobacco abstinence through gradual reduction could engage more smokers in quitting.5-7

Among cigarette smokers not ready to quit, tobacco reduction incorporating nicotine replacement therapy and behavioral interventions decreases cigarettes smoked and increases future smoking abstinence.6-9 Population-based studies suggest that quitting gradually may be less successful than quitting abruptly.9 However, a systematic review comparing both approaches suggests that reducing cigarettes before the quit date and quitting abruptly without prior reduction yields comparable quit rates.9

Almost all prior studies of pharmacotherapy-aided reduction have examined nicotine replacement therapies. Varenicline is a partial agonist binding with high affinity and selectivity at α4β2 neuronal nicotinic acetylcholine receptors.10 Varenicline significantly increases smoking abstinence rates among smokers seeking treatment and quitting abruptly.11,12 Among smokers not trying to stop, varenicline significantly reduces cigarette consumption13 and may increase quit attempts.14 Varenicline may be an effective intervention for smokers who are not willing or able to make an immediate quit attempt but who would be willing to reduce their smoking in preparation for a quit attempt in the future (ie, a “reduce-to-quit” approach). A prior reduce-to-quit study of varenicline was small, provided only 8 weeks of varenicline, and obtained equivocal results.14 We conducted a larger, randomized, placebo-controlled clinical trial providing varenicline for 6 months to evaluate a “reduce-to-quit” approach.

Methods

Study Design

Written consent forms and study procedures were approved by the institutional review boards or ethics committees of participating institutions and each enrolled participant voluntarily signed the consent form. A randomized, double-blind, placebo-controlled trial was conducted at 61 centers in 10 countries (Australia, Canada, Czech Republic, Egypt, Germany, Japan, Mexico, Taiwan, United Kingdom, and United States) between July 2011 and July 2013. Study sites included clinical trial centers, academic centers, and outpatient clinics. Study site training was provided at an investigator meeting with training materials maintained and accessible through a shared website. The study consisted of a 24-week treatment period followed by a 28-week nontreatment follow-up phase (protocol in Supplement 1). The first 12 weeks of treatment were the reduction phase and the next 12 weeks were the abstinence phase. Participants were recruited through advertising. Recruitment advertisements included the following language: “Want to quit smoking but prefer to cut down first?” and “Are you ready to quit but prefer to do it gradually?” and “Want to quit smoking, but hate the idea of going cold turkey?” Enrollment ended when recruitment goals were achieved. Participants received financial compensation for time spent for clinic and phone visits as well as travel time; the amount of remuneration was determined by each clinical trial site.

Screening and Eligibility Criteria

Eligible participants were 18 years or older, smoked an average of 10 or more cigarettes per day with no continuous abstinence period longer than 3 months in the past year, had an exhaled carbon monoxide level higher than 10 ppm, and were not willing or able to quit smoking within the next month but were willing to reduce their smoking and make a quit attempt within the next 3 months.

Exclusion criteria included a history of a suicide attempt or suicidal behavior in the previous 2 years as assessed by the Columbia-Suicide Severity Rating Scale (C-SSRS)9 and the Suicide Behavior Questionnaire-Revised (SBQ-R)16; major depressive or anxiety disorder assessed by a physician as severe (lifetime or current) or unstable (ie, medication dose change or exacerbations in the last 6 months); lifetime diagnosis of psychosis, panic disorder, posttraumatic stress disorder, or schizophrenia; alcohol or substance abuse in the last 12 months; a diagnosis of severe chronic obstructive pulmonary disease; clinically significant cardiovascular or cerebrovascular disease in the previous 2 months; taking more than a limited number of doses of varenicline previously; and self-reported inability to abstain from noncigarette tobacco products, marijuana, or smoking cessation aids (including electronic cigarettes). Women were excluded if pregnant, lactating, or likely to become pregnant and unwilling to use contraception.

Study Procedures

Participants were randomized to receive varenicline or placebo for 24 weeks of treatment in a 1:1 ratio using a computer-generated block randomization schedule within site (Figure 1). Investigators obtained participant identification numbers and treatment group assignments through a web-based or telephone call-in drug management system. Participants, investigators, and research personnel were blinded to randomization until after the database was locked.

Race/ethnicity was self-reported. At each clinic visit and telephone contact, information was collected on cigarette or other nicotine product use. Exhaled carbon monoxide measurements were obtained at all clinic visits. Tobacco dependence was assessed with the Fagerström Test for Nicotine Dependence.17 Study design is shown in the eFigure in Supplement 2.

Adverse events and US Food and Drug Administration defined serious adverse events (adverse events resulting in death, hospitalization, or other important medical events) were collected during study visits during the treatment phase and up to 1 month after last treatment dose. A semistructured interview solicited information about psychiatric adverse events. Suicidal ideation and behavior were assessed using the C-SSRS.
Interventions
Participants were asked to reduce their baseline smoking rate by 50% or more by week 4 with further reduction to 75% or more from baseline by week 8 with the goal of quitting by week 12. Counseling training was provided at the investigator meet-
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Participants started with a recommended varenicline (or matching placebo) dosage of 0.5 mg once daily for 3 days, increasing to 0.5 mg twice daily for days 4 to 7, and then to the maintenance dose of 1 mg twice daily.

Study End Points
The primary efficacy end point was the carbon monoxide–confirmed continuous abstinence rate (CAR) during the last 10 weeks of treatment (ie, weeks 15-24). A participant was considered abstinent from tobacco if he or she self-reported tobacco abstinence throughout the period and had an exhaled carbon monoxide level of 10 ppm or less at each visit. In the case of a missing visit, participants were considered abstinent if they were abstinent at the next nonmissed visit and also reported not smoking during the missed visit. A missing carbon monoxide measurement did not disqualify a participant from meeting the end point if they self-reported not smoking. Secondary efficacy end points were the CARs during weeks 21 through 24 and during weeks 21 through 52. We also calculated the nonprespecified end point of the CAR for weeks 15 through 52.

Results
Enrollment and Follow-up
Of 1747 potentially eligible participants screened, 1510 (86%) were randomly assigned to receive varenicline (n = 760) or placebo (n = 750). Overall study completion was defined as completion of the week 52 visit and was 73.6% (559 of 760 participants) in the varenicline group and 68.8% (516 of 750 participants) in the placebo group (Figure 1). Participants assigned to study groups were similar in demographic and smoking characteristics at baseline (Table 1). Participants who discontinued treatment were encouraged to remain in the study.

Smoking Abstinence
The varenicline group (n = 760) had significantly higher continuous abstinence rates during weeks 15 through 24 than the placebo group (n = 750) (32.1% for the varenicline group vs 25.2% for the placebo group; RD, 25.2% [95% CI, 21.1%-29.0%]; RR, 1.24 [95% CI, 1.16-1.32]) and weeks 21 through 52 (27.0% for the varenicline group vs 20.6% for the placebo group; RD, 26.4% [95% CI, 21.1%-31.7%]; RR, 1.33 [95% CI, 1.19-1.49]). No significant differences in adverse events were observed between groups.

A logistic regression model included treatment effect as the explanatory variable and investigational center as a covariate. In addition, an expanded logistic regression model including the treatment-by-center interaction was used to test for the interaction effect. However, as prespecified in the statistical analysis plan, the inferences were based solely on the prespecified logistic regression model including only the main effects of treatment and center, regardless of the significance of the treatment-by-center interaction (with P ≤ .05 considered significant). Relative risks (RRs) and risk differences (RDs) calculated using Proc Freq (SAS Institute) with option RELRISK (for RRs) and RISKDIFF (for RDs) are reported for efficacy end points. We conducted a sensitivity analysis for the primary end point in which participants who were missing a carbon monoxide measurement during weeks 15 through 24 were classified as smokers.

To preserve the type I familywise error rate of .05, a fixed-sequence procedure was used. The treatment comparison was performed first for weeks 15 through 24, then for weeks 21 through 24, and then for weeks 21 through 52. A post hoc analysis was conducted in the same manner for the end point of the CAR for weeks 15 through 52. Each test used a 2-sided P value of .05 or less for significance. We used SAS (SAS Institute), version 9.2, for statistical analyses.

Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 16.1.22 Adverse events occurring during treatment and up to 30 days after receiving the last dose of study drug are reported. All safety analyses included all randomized participants who received any dose of study medication. Our study was not powered to detect significant differences in adverse events between groups.

Statistics
The efficacy analysis was based on the intent-to-treat population (all randomized participants). Participants who dropped out of the study were treated as smokers. A sample size of 1404 randomized participants in a 1:1 ratio (702 in each group) was estimated to provide 90% or more power to detect a difference between varenicline and placebo of 10.3% in the primary end point of CAR during weeks 15 through 24, assuming a CAR of 17.2% for varenicline and 6.9% for placebo using a 2-group, continuity–corrected, 2-sided χ² test. A P value of .05 or less was considered significant.3,19,20
significant treatment-by-center interaction for the primary end point was observed in the logistic regression model.

Among the 244 participants receiving varenicline who were counted as abstinent for the primary end point, there were 25 participants with at least 1 missing carbon monoxide measurement (including those with missing visits) during weeks 15 through 24; among the 52 participants receiving placebo who met the primary end point, there were 4 participants with at least 1 missing carbon monoxide measurement. We conducted a sensitivity analysis with participants who were missing a carbon monoxide measurement being classified as smokers for the weeks 15 through 24 continuous abstinence rate (219 participants [28.8%] for varenicline vs 48 participants [6.4%] for placebo). The RR for this analysis was 4.5 (95% CI, 3.4-6.1). This value approximates the value we observed using the prespecified imputation (RR, 4.6 [95% CI, 3.5-6.1]). Among participants meeting the primary end point (abstinent during weeks 15-24), the median time from baseline to the beginning of the continuous abstinence period was 50 days for varenicline and 85 days for placebo (P < .001). The varenicline group also had a significantly higher 7-day point prevalence smoking abstinence rate compared with placebo at weeks 12, 24, and 52 (Figure 2). Varenicline significantly increased the 4-week point prevalence smoking abstinence rate compared with placebo at week 52 (32.8% for varenicline vs 17.3% for placebo; RD, 15.4% [95% CI, 11.1%-19.7%]; RR, 1.9 [95% CI, 1.6-2.3]).

Smoking Reduction (Weeks 1 to 12)
At week 4, 47.1% of participants treated with varenicline (358 of 760 participants) reduced the number of cigarettes smoked per day (ie, average number of cigarettes during days on which smoking occurred over the last week) compared with baseline by 50% or more or abstained completely compared with 31.1% of participants treated with placebo (233 of 750 participants) (RD, 16.0% [95% CI, 11.2%-20.9%]; RR, 1.5 [95% CI, 1.3-1.7]). After 8 weeks, 26.3% participants in the varenicline group (200 of 760 participants) reduced smoking by 75% or more from baseline or abstained compared with 15.1% participants in the placebo group (113 of 750 participants) (RD, 11.3% [95% CI, 7.2%-15.3%]; RR, 1.8 [95% CI, 1.4-2.2]).

Safety
The percentage of participants with adverse events was higher in the varenicline group than in the placebo group (618 of 751 participants [82.3%] in the varenicline group vs 538 of 742 participants [72.5%] in the placebo group). Adverse events with the greatest risk difference between varenicline and placebo (≥2%) were nausea, abnormal dreams, insomnia, constipation, vomiting, and weight gain (Table 3). Adverse event incidence resulting in permanent treatment discontinuation was not significantly different between the 2 groups (63 of 751 participants [8.4%] in the varenicline group vs 52 of 742 participants [7.0%] in the placebo group; P = .27). Percentages of participants with serious adverse events were not significantly different between varenicline and placebo (28 of 751 participants [3.7%] in the varenicline group vs 16 of 742 participants [2.2%] in the placebo group; P = .07). During treatment and up to 30 days after the last dose, suicidal ideation or behavior was recorded on the C-SSRS in 6 of 751 participants (0.8%) in the varenicline group and 10 of 742 participants (1.3%) in the placebo group. Any increases in PHQ-9 depression scores from baseline to any time point after baseline occurred in 169 of 751 participants (22.5%) treated with varenicline compared with 145 of 742 participants (19.5%) treated with placebo (P = .16).

Discussion
Among cigarette smokers not willing or able to quit smoking in the next month but willing to reduce with the goal of quitting in the next 3 months, varenicline produced a statistically and clinically significant increase in the CARs at the end of treatment and at 28 weeks after treatment. Varenicline produced greater smoking reduction than placebo prior to quitting. Varenicline was not associated with significant increases in treatment discontinuations due to adverse events.

Smokers enrolled in the current study were not ready to quit in the next month, and overall smoking abstinence rates would

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Table 1. Participant Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Varenicline Group (n = 760)</th>
<th>Placebo Group (n = 750)</th>
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<tbody>
<tr>
<td><strong>Demographic Characteristics</strong></td>
<td></td>
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<tr>
<td>Sex, No. (%)</td>
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<tr>
<td>Men</td>
<td>425 (55.9)</td>
<td>426 (56.8)</td>
</tr>
<tr>
<td>Women</td>
<td>335 (44.1)</td>
<td>324 (43.2)</td>
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<tr>
<td>Age, mean (SD) [range], y</td>
<td>44.7 (11.8) [19-79]</td>
<td>44.4 (12.0) [18-78]</td>
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<tr>
<td>Race/ethnicity, No. (%)</td>
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<tr>
<td>White</td>
<td>476 (62.6)</td>
<td>463 (61.7)</td>
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<td>Black</td>
<td>36 (4.7)</td>
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<td>177 (23.6)</td>
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<tr>
<td>Other</td>
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<td><strong>Smoking characteristics, mean (SD)</strong></td>
<td></td>
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<tr>
<td>Fagerström Test for Nicotine Dependence scorea</td>
<td>5.5 (2.1)</td>
<td>5.6 (2.0)</td>
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<tr>
<td>Age started smoking, y</td>
<td>17.3 (4.3)</td>
<td>17.3 (4.4)</td>
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<tr>
<td>No. of cigarettes per day in past month</td>
<td>20.6 (8.5)</td>
<td>20.8 (8.2)</td>
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<td><strong>Longest Period of Abstinence</strong></td>
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<td>Since started smoking, d</td>
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<tr>
<td>Median (IQR)</td>
<td>30 (3-240)</td>
<td>21 (2-180)</td>
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<tr>
<td>Mean</td>
<td>272</td>
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<td>In past year, d</td>
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<tr>
<td>Median (IQR)</td>
<td>0 (0-1)</td>
<td>0 (0-0)</td>
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<tr>
<td>Mean</td>
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<td>3</td>
</tr>
<tr>
<td><strong>No. of Serious Quit Attempts by Any Method</strong></td>
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<tr>
<td>Since started smoking, No. (%)</td>
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<tr>
<td>None</td>
<td>130 (17.1)</td>
<td>159 (21.2)</td>
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<tr>
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<td>191 (25.1)</td>
<td>188 (25.1)</td>
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<tr>
<td>≥3</td>
<td>300 (39.5)</td>
<td>293 (39.1)</td>
</tr>
</tbody>
</table>

Abbreviation: IQR, interquartile range.

a Fagerström Test for Nicotine Dependence measures the degree of cigarette dependence with scores ranging from 0 to 10 with higher scores indicating a higher degree of dependence.17
have been expected to be low. Although overall smoking abstinence rates were low in the placebo group, varenicline increased the rates of achieving abstinence such that the absolute abstinence rates were similar to those observed in studies of varenicline in smokers motivated to quit after 1 week of treatment.\(^1\)\(^\text{11}\)\(^\text{12}\)

The mechanism of varenicline action as an aid to gradual cessation could relate to a reduction in cigarette craving or a blockade of the reinforcing action of nicotine through partial agonist activity at the nicotinic acetylcholine receptors.\(^1\)\(^\text{10}\) Ancillary effects from varenicline may exist with respect to confidence in ability to quit. However, this should have been controlled through study blinding and any effect via this route is likely to be small given limited evidence that confidence plays a causal role in sustaining quitting attempts.\(^2\)\(^\text{22}\)

Adverse events caused by varenicline were similar to previous observations. In the present study, varenicline was associated with an increased rate of constipation and weight gain. However, both are established effects of smoking cessation,\(^2\)\(^\text{3}\)\(^\text{,}2\)\(^\text{4}\) and it is possible that the greater incidence of abstinence with varenicline and not the direct effect of varenicline was the cause. The incidence of bronchitis was lower in those treated with varenicline, an effect which is possibly mediated by an increased rate of smoking cessation.\(^2\)\(^\text{5}\) Varenicline did not increase the risk of suicidal ideation or behavior or other psychiatric adverse events.

Major strengths of this study include the randomized design, large sample size, and convergent validity of the findings across multiple outcomes and measures. One limitation of this study relates to the exclusion of potential participants if they had severe psychiatric, pulmonary, cardiovascular, or cerebrovascular disease. As a result, the generalizability of this treatment approach to a broader population of smokers who need to quit smoking but may want to achieve it through reduction is unknown. In addition, participants in the current study were provided with significant support with counseling from trained staff occurring during 18 clinic and 10 telephone visits. Because of this, the observed abstinence rates with varenicline in actual clinical practice might be expected to be less than that observed in the current trial. We did not test whether varenicline would be more effective for the reduce-to-quit cessation approach than other tobacco treatments such as nicotine replacement therapy.

Uncertainty remains as to the prevalence of smokers in the general population who meet the definition of smokers enrolled in this study. In a cross-sectional study collecting data via telephone or face-to-face interview with daily smokers responding to the Current Population Survey, the prevalence of contemplators (ie, interested in quitting smoking in next 6
months but not in the next 30 days) was 33.2%. We were not attempting to fit smokers into a specific stage of readiness for behavior change. Instead, our approach aimed to reduce barriers to engaging in the quitting process by allowing and facilitating smoking reduction in a precessation phase. Our sample most closely resembles the 33% of smokers who want to quit sometime between 1 and 6 months in the future. The approach used in this study would be expected to be of interest to 14 million of the 42 million current smokers.

The US Public Health Service and other guidelines recommend smokers set a quit date in the near future and quit abruptly. However, many smokers may be unwilling to commit to a quit date at a clinic visit. Because most clinicians are likely to see smokers at times when a quit date in the next month is not planned, the current study indicates that prescription of varenicline with a recommendation to reduce the number of cigarettes smoked per day with the eventual goal of quitting could be a useful therapeutic option for this population of smokers. The approach of reduction with the goal of quitting increases the options for a clinician caring for a smoker.

### Conclusions

Among cigarette smokers not willing or able to quit within the next month but willing to reduce cigarette consumption and make a quit attempt at 3 months, use of varenicline for 24 weeks compared with placebo significantly increased smoking cessation rates at the end of treatment, and also at 1 year. Varenicline offers a treatment option for smokers whose needs are not addressed by clinical guidelines recommending abrupt smoking cessation.
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ARTICLE INFORMATION

Author Contributions: Drs Ebbert and Yu had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Hughes, West, Rennard, Ross, Treadow, Yu, Park.

Acquisition, analysis, or interpretation of data: Ebbert, Hughes, West, Rennard, Russia, McRae, Treadow, Yu, Dutto.

Drafting of the manuscript: Ebbert, Hughes, West, Rennard, Russia, McRae, Treadow, Yu, Dutto.

Critical review of the manuscript for important intellectual content: Ebbert, Hughes, Rennard, Russia, Yu, Dutto, Park.

Statistical analysis: Yu.

Obtained funding: Park.

Administrative, technical, or material support: Treadow, Dutto, Park.

Study supervision: Treadow, Dutto, Park.

Conflicts of Interest: The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Ebbert reports receiving grants from JHP Pharmaceuticals, Orexigen, Pfizer, and the National Institutes of Health; and receiving personal fees from GlaxoSmithKline during the conduct of the study. Dr Hughes reports receiving personal fees from Alera/Free and Clear, CicateLL, DLA Piper, Dorfnermeyer, Embra, Equinox, GlaxoSmithKline, Healthwise, Nicoventures, Pfizer, Pro Ed, Publicis, Selecta, and nonfinancial support from Swedish Match. Dr West reports receiving grants, personal fees, and nonfinancial support from Pfizer, GlaxoSmithKline, and Johnson & Johnson. His salary is funded by a Centre grant from Cancer Research UK. Dr Rennard reports being an advisory board member for A2B Bio, Almirall, Dalichi Sankryo, Novartis, NymcoMed, and Pfizer; consulting for Almirall, APT Pharma/Britannia, AstraZeneca, Boehringer Ingelheim, Chiesi, CSL Behring, Decision Resource, Dunn Group, Easton Associates, Gerson, GlaxoSmithKline, Medimmune, Novartis, Pearl, Roche, Takeda, and Theravance; receiving lecture fees from CME Incite, Forest, Novis, PriMed, and Takeda; receiving grants from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Johnson & Johnson, Novartis, and Otsuka. Drs Ross, McRae, Yu, Dutto, Park, and Ms Treadow are employees and stockholders of Pfizer.

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REFERENCES


