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 end point 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

Forty percent of cigarette smokers make an average of 2 quit attempts annually. 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. However, US clinical practice guidelines recommend that smokers quit abruptly even though only 8% of smokers report being ready to quit in the next month. Developing effective interventions to achieve tobacco abstinence through gradual reduction could engage more smokers in quitting.

Among cigarette smokers not ready to quit, tobacco reduction incorporating nicotine replacement therapy and behavioral interventions decreases cigarettes smoked and increases future smoking abstinence. Population-based studies suggest that quitting gradually may be less successful than quitting abruptly. 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.

Almost all prior studies of pharmacotherapy-aided reduction have examined nicotine replacement therapies. Varenicline is a partial agonist binding with high affinity and selectivity to α4β2 neuronal nicotinic acetylcholine receptors. Varenicline significantly increases smoking abstinence rates among smokers seeking treatment and quitting abruptly. Among smokers not trying to stop, varenicline significantly reduces cigarette consumption and may increase quit attempts.

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. 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) and the Suicide Behavior Questionnaire-Revised (SBQ-R); 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. 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.
at baseline and all study visits. Participants completed the Patient Health Questionnaire (PHQ)-9 to assess the frequency and severity of potential depression-related events every other week during the treatment phase and at clinic visits during the follow-up phase.

**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-
ing. Smoking cessation counseling was provided consistent with the recommendations of the US Department of Health and Human Services “Treating Tobacco Use and Dependence” clinical practice guideline. Participants received the Clearing the Air: Quit Smoking Today booklet from the National Cancer Institute. Advice on reduction techniques was provided such as systematically increasing the amount of time between cigarettes and rank-ordering and then eliminating cigarettes from easiest to hardest to give up. Counseling was tailored to the participant’s needs during the reduction, abstinence, and post-treatment phases. Counsellors were urged to be consistent and brief, to focus on problem solving (eg, what triggers the urge to smoke) and skills training (eg, practical actions to avoid smoking), and to highlight successes not failures. Individual counseling lasted 10 minutes or less per visit during 18 clinic and 10 telephone visits. The last cigarette was to be smoked prior to midnight on the day before the week 12 visit. Participants could reduce their smoking faster and could make a quit attempt before week 12. Participants who had not reduced or made a quit attempt by week 12 were encouraged to continue medications and visits and make quit attempts, and participants who relapsed after week 12 were encouraged to make new quit attempts. After the 24-week treatment phase (ie, 12 weeks of reduction and 12 weeks after a quit attempt) participants were followed up through week 52 (28-week nontreatment phase). Patients who relapsed after week 12 were encouraged to make new quit attempts. After the 24-week treatment phase (ie, 12 weeks of reduction and 12 weeks after a quit attempt) participants were followed up through week 52 (28-week nontreatment follow-up phase).

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.

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 $\chi^2$ test. A P value of .05 or less was considered significant.6,19,20

A logistic regression model included treatment effect as the explanatory variable and investigative 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 fixedsequence 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 16.1.21 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.

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 21.5% for the placebo group; RD, 25.2% [95% CI, 21.4%-29.0%]; RR, 4.7 [95% CI, 3.5-6.1]) (Table 2). 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]). No
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]).

**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 timepoint 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
agonist activity at the nicotinic acetylcholine receptors. An blockade of the reinforcing action of nicotine through partial cessation could relate to a reduction in cigarette craving or a nencerate were similar to those observed in studies of vareni- rates of achieving abstinence such that the absolute abstinence rates were lower in the placebo group, varenicline increased effective for the reduce-to-quit cessation approach than other tobacco treatments such as nicotine replacement therapy.

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 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

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<th>Table 2. Continuous Carbon Monoxide–Confirmed Smoking Abstinence Rates for Periods of the Studya</th>
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<td>Continuous Abstinence, No. of Participants (%)</td>
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<td>Varenicline Group (n = 760)</td>
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<td>Placebo Group (n = 750)</td>
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<td>Risk Difference, % (95% CI)</td>
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<td>Relative Risk (95% CI)</td>
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<td>Primary End Pointb</td>
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<td>Weeks 15-24</td>
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<td>244 (32.1)</td>
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<td>52 (6.9)</td>
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<td>25.2 (21.4-29.0)</td>
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<td>4.6 (3.5-6.1)</td>
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<td>Secondary End Pointsb</td>
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<td>Weeks 21-24</td>
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<td>287 (37.8)</td>
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<td>Weeks 21-52</td>
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<td>182 (24.0)</td>
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<td>18.0 (14.5-21.4)</td>
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<td>4.0 (2.9-5.4)</td>
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* All randomized participants were included at all time points. For nonmissed visits, a carbon monoxide level higher than 10 ppm disqualified participants from meeting the end point. Participants with missing carbon monoxide measurements met the end point if they self-reported not smoking. Participants with missing visits were considered abstinent if they self-reported not smoking and did not have a carbon monoxide measurement higher than 10 ppm at the next nonmissed visit and also reported not smoking during the missed visit. Participants who withdrew from the study were considered smokers after the time of withdrawal.

**b** The primary endpoint was carbon monoxide–confirmed self-reported abstinence during weeks 15 through 24; secondary end points, carbon monoxide–confirmed self-reported abstinence for weeks 21 through 24 and weeks 21 through 52; post hoc end point, carbon monoxide–confirmed self-reported abstinence for weeks 15 through 52.

Figure 2. Seven-Day Point Prevalence Smoking Abstinence for Participants Receiving Varenicline vs Placebo

RD indicates risk difference; RR, relative risk.

Week 12: RD, 24.5% (95% CI, 20.8%-28.3%), RR, 4.7 (95% CI, 3.5-6.2); week 24: RD, 25.7% (95% CI, 21.2%-30.3%), RR, 2.5 (95% CI, 2.1-3.0); week 52: RD, 15.8% (95% CI, 11.5%-20.2%), RR, 1.9 (95% CI, 1.6-2.2).

All randomized participants were included at all time points. For nonmissed visits, carbon monoxide level higher than 10 ppm disqualified participants from meeting the end point when abstinence was self-reported. Participants with missing carbon monoxide measurements met the end point if they self-reported smoking abstinence. Participants with missing visits were considered smokers for that visit. Participants who withdrew from the study were considered smokers from the time of withdrawal. Error bars indicate 95% CIs.

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. 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...
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.
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, Russ, Treadow, Yu, Park.

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

Drafting of the manuscript: Ebbert, Hughes, West, Rennard, Russ, McRae, Treadow, Yu, Dutro.

Critical revision of the manuscript for important intellectual content: Ebbert, Hughes, Rennard, Russ, Yu, Dutro, Park.

Statistical analysis: Yu.

Obtained funding: Yu, Dutro, Park.

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

Study supervision: Treadow, Dutro, Park.

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REFERENCES


