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# Cytisinicline for Smoking Cessation

## A Randomized Clinical Trial

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**IMPORTANCE** Cytisinicline (cytisine) is a plant-based alkaloid that, like varenicline, binds selectively to  $\alpha 4\beta 2$  nicotinic acetylcholine receptors, which mediate nicotine dependence. Although not licensed in the US, cytisinicline is used in some European countries to aid smoking cessation, but its traditional dosing regimen and treatment duration may not be optimal.

**OBJECTIVE** To evaluate the efficacy and tolerability of cytisinicline for smoking cessation when administered in a novel pharmacokinetically based dosing regimen for 6 or 12 weeks vs placebo.

**DESIGN, SETTING, AND PARTICIPANTS** A 3-group, double-blind, placebo-controlled, randomized trial (ORCA-2) compared 2 durations of cytisinicline treatment (6 or 12 weeks) vs placebo, with follow-up to 24 weeks, among 810 adults who smoked cigarettes daily and wanted to quit. It was conducted at 17 US sites from October 2020 to December 2021.

**INTERVENTIONS** Participants were randomized (1:1:1) to cytisinicline, 3 mg, 3 times daily for 12 weeks (n = 270); cytisinicline, 3 mg, 3 times daily for 6 weeks then placebo 3 times daily for 6 weeks (n = 269); or placebo 3 times daily for 12 weeks (n = 271). All participants received behavioral support.

**MAIN OUTCOMES AND MEASURES** Biochemically verified continuous smoking abstinence for the last 4 weeks of cytisinicline treatment vs placebo (primary) and from end of treatment to 24 weeks (secondary).

**RESULTS** Of 810 randomized participants (mean age, 52.5 years; 54.6% female; mean of 19.4 cigarettes smoked daily), 618 (76.3%) completed the trial. For the 6-week course of cytisinicline vs placebo, continuous abstinence rates were 25.3% vs 4.4% during weeks 3 to 6 (odds ratio [OR], 8.0 [95% CI, 3.9-16.3];  $P < .001$ ) and 8.9% vs 2.6% during weeks 3 to 24 (OR, 3.7 [95% CI, 1.5-10.2];  $P = .002$ ). For the 12-week course of cytisinicline vs placebo, continuous abstinence rates were 32.6% vs 7.0% for weeks 9 to 12 (OR, 6.3 [95% CI, 3.7-11.6];  $P < .001$ ) and 21.1% vs 4.8% during weeks 9 to 24 (OR, 5.3 [95% CI, 2.8-11.1];  $P < .001$ ). Nausea, abnormal dreams, and insomnia occurred in less than 10% of each group. Sixteen participants (2.9%) discontinued cytisinicline due to an adverse event. No drug-related serious adverse events occurred.

**CONCLUSIONS AND RELEVANCE** Both 6- and 12-week cytisinicline schedules, with behavioral support, demonstrated smoking cessation efficacy and excellent tolerability, offering new nicotine dependence treatment options.

**TRIAL REGISTRATION** ClinicalTrials.gov Identifier: [NCT04576949](https://clinicaltrials.gov/ct2/show/study/NCT04576949)

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Cigarette smoking is the leading preventable cause of premature mortality worldwide.<sup>1</sup> Individuals who stop tobacco use reduce their health risks and increase life expectancy.<sup>2,3</sup> Those who use a smoking cessation medication, such as nicotine replacement, bupropion, or varenicline, increase their odds of achieving sustained abstinence when attempting to quit.<sup>4-7</sup> However, these US Food and Drug Administration (FDA)-approved pharmacotherapies have modest long-term abstinence rates and are associated with adverse events that may discourage their use.<sup>6</sup> No smoking cessation pharmacotherapy has received FDA approval since 2006.<sup>8</sup> New options are needed.

Cytisinicline, historically known as cytisine, is a naturally occurring plant-based alkaloid that has been used as an over-the-counter smoking cessation product in Central and Eastern Europe for decades but is not approved for marketing and labeling by regulatory agencies in countries outside this region.<sup>9,10</sup> Cytisinicline, like varenicline, binds selectively to the  $\alpha 4\beta 2$  nicotinic acetylcholine receptor subtype that mediates nicotine dependence, acting as a partial agonist to reduce nicotine withdrawal symptoms while also blocking the reinforcement generated by nicotine when smoking cigarettes.<sup>9</sup>

The manufacturers' recommended cytisine dosage is 1.5-mg tablets initially taken 6 times daily then gradually reduced over a 25-day course of treatment. With this regimen, cytisine demonstrated higher smoking cessation efficacy than placebo in a double-blind, randomized clinical trial in Poland<sup>11</sup> and greater effectiveness than a nicotine patch in an open-label, randomized clinical trial in New Zealand.<sup>12</sup> In a randomized, open-label, noninferiority trial in Australia among individuals who smoked daily and were willing to quit, a trial of cytisine treatment for 25 days, compared with varenicline treatment for 84 days, failed to demonstrate noninferiority regarding smoking cessation.<sup>13</sup> No serious safety issues were identified in these trials or during the decades of commercial use in Europe.<sup>9-13</sup>

However, the scientific rationale for this regimen has never been published and may not be optimal.<sup>9</sup> Cytisinicline's mean elimination half-life of 4.8 hours supports a simplified regimen using 3 times daily administration.<sup>9,14</sup> In a randomized phase 2b trial testing various doses and schedules for 25 days, 3 mg administered 3 times daily produced the highest biochemically confirmed continuous abstinence during 4 consecutive weeks after treatment ended (weeks 4 to 8) and was superior to placebo (30% vs 8%,  $P = .005$ ).<sup>15</sup> The 3-mg dose taken 3 times daily was well tolerated, achieved good treatment adherence, and was selected for use in phase 3 clinical trials.<sup>15</sup>

Because relapse commonly occurs early in a quit attempt, a treatment duration longer than 25 days might improve the effectiveness of the revised cytisinicline regimen.<sup>9,16</sup> This randomized, double-blind, clinical trial compared the efficacy and tolerability of cytisinicline, 3 mg, administered 3 times daily vs placebo when administered for 6 weeks or 12 weeks.

## Methods

This multisite, 3-group, double-blind, randomized phase 3 clinical trial evaluated the efficacy and tolerability of cytisini-

## Key Points

**Question** Is cytisinicline an effective and safe pharmacotherapy to promote smoking cessation?

**Findings** In a randomized clinical trial that included 810 adults who smoked, both a 6-week and a 12-week course of a novel cytisinicline dosing regimen were more effective than placebo and were well tolerated, producing significantly higher continuous smoking abstinence rates compared with placebo during the last 4 weeks of drug treatment and from the end of treatment to 24 weeks.

**Meaning** Both 6- and 12-week cytisinicline schedules, with behavioral support, demonstrated smoking cessation efficacy and excellent tolerability, offering a new nicotine dependence treatment option.

cline vs placebo, accompanied by behavioral support, for smoking cessation. The trial was approved by a centralized institutional review board. Participants provided written informed consent and were randomized from October 2020 through June 2021. Data collection ended in December 2021. Full protocol details are in the trial protocol ([Supplement 1](#)) and summarized here. The statistical analysis plan is in [Supplement 2](#).

## Setting and Participants

The trial was conducted at 17 sites widely distributed across the US, with the largest number of sites in the Southeast. Adults aged 18 years or older were eligible if they currently smoked 10 or more cigarettes per day, had expired air carbon monoxide (CO) greater than or equal to 10 ppm, and were ready to set a date to quit smoking ([Table 1](#) and [Figure 1](#)). Individuals were excluded if they used any noncigarette tobacco product (pipe tobacco, cigars, smokeless tobacco, hookah), electronic cigarettes, smoking cessation medication (bupropion, varenicline, nortriptyline, nicotine replacement product), or marijuana (smoked or vaped) in the 28 days before randomization or planned to use them during the study. Other exclusion criteria included uncontrolled hypertension; hepatic or kidney impairment; 3-month history of acute myocardial infarction, unstable angina, cerebrovascular incident, or hospitalization for congestive heart failure; moderate to severe depression symptoms (Hospital Anxiety and Depression Scale score  $\geq 11$ )<sup>18</sup>; diagnosis of schizophrenia or bipolar disorder, current psychosis, suicidal ideation, or suicide risk (Columbia Suicide Severity Rating Scale)<sup>19</sup>; or a positive urinary screen for illicit drugs. (Full criteria are in the trial protocol in [Supplement 1](#)).

## Recruitment and Assignment to Condition

At a screening visit, individuals provided written informed consent; completed a medical history, brief physical examination, and electrocardiogram and laboratory tests; agreed to a quit date 5 to 7 days after study drug initiation; and recorded the number of cigarettes smoked daily for 7 days. Baseline measures included race and ethnicity, assessed by a participant's response to a fixed-category question, in order to explore

Table 1. Baseline Characteristics of Study Participants by Treatment Group

Demographic	Cytisinicline for 12 wk (n = 270)	Cytisinicline for 6 wk (n = 269)	Placebo (n = 271)
Age, mean (SD), y	53.3 (11.6)	52.2 (11.2)	52.0 (12.0)
Sex, No. (%)			
Male	135 (50.0)	121 (45.0)	112 (41.3)
Female	135 (50.0)	148 (55.0)	159 (58.7)
Race, No. (%) <sup>a</sup>			
American Indian/ Alaska Native	1 (0.4)	2 (0.7)	1 (0.4)
Asian	1 (0.4)	1 (0.4)	1 (0.4)
Black or African American	48 (17.8)	40 (14.9)	42 (15.5)
Native Hawaiian or Other Pacific Islander	1 (0.4)	1 (0.4)	2 (0.7)
White	216 (80.0)	222 (82.5)	221 (81.5)
Other	3 (1.1)	3 (1.1)	4 (1.5)
Hispanic ethnicity, No. (%)	23 (8.5)	26 (9.7)	19 (7.0)
Tobacco use, mean (SD)			
Duration of smoking, y	37.0 (12.9)	36.3 (12.7)	36.5 (12.6)
Cigarettes per day in the past 30 d	19.4 (7.2)	19.4 (7.3)	19.4 (7.7)
Expired air carbon monoxide, ppm	26.4 (14.5)	26.3 (14.7)	26.6 (13.8)
Fagerstrom Test for Nicotine Dependence score <sup>b</sup>	5.6 (1.9) [n = 269]	5.5 (1.8) [n = 267]	5.6 (1.7)
Quitting history			
Prior quit attempts, median (IQR)	4 (2-6)	4 (3-6)	4 (2-6)
Prior cessation medication used, No. (%)			
Nicotine replacement product	174 (64.4)	167 (62.1)	171 (63.1)
Varenicline	127 (47.0)	113 (42.0)	114 (42.1)
Bupropion	57 (21.1)	40 (14.9)	56 (20.7)
Prior cessation behavioral support used, No. (%) <sup>c</sup>	30 (11.1)	25 (9.3)	23 (8.5)
Comorbidities			
Hospital Anxiety and Depression Scale total score, mean (SD) <sup>d</sup>	5.5 (4.5)	5.4 (3.7)	5.5 (4.2)

<sup>a</sup> Race and ethnicity were assessed by a participant's response to a fixed-category question.

<sup>b</sup> Fagerstrom Test for Nicotine Dependence<sup>17</sup> is a 6-item self-administered scale with a range of scores 0 to 10. Higher scores indicate greater physical dependence on nicotine, which is associated with less success achieving abstinence during a quit attempt.

<sup>c</sup> Includes counseling support received in person, by phone, or via web.

<sup>d</sup> Hospital Anxiety and Depression Scale<sup>18</sup> is a 14-item self-administered scale, with a range of scores 0 to 42. Higher scores indicate more symptoms of anxiety and depression.

whether these factors moderated treatment success. At a second visit, participants who met inclusion and exclusion criteria were randomly assigned to a study group, received brief smoking cessation counseling, set their quit date within 5 to 7 days, and started study medication the next day. A predetermined central computer-generated randomization sequence was used to assign participants (1:1:1) stratified by study site to receive placebo 3 times daily for 12 weeks, 3-mg cytisinicline 3 times daily for 6 weeks followed by placebo 3 times daily for 6 weeks, or 3-mg cytisinicline 3 times daily for 12 weeks (eFigure 1 in Supplement 3).

### Interventions

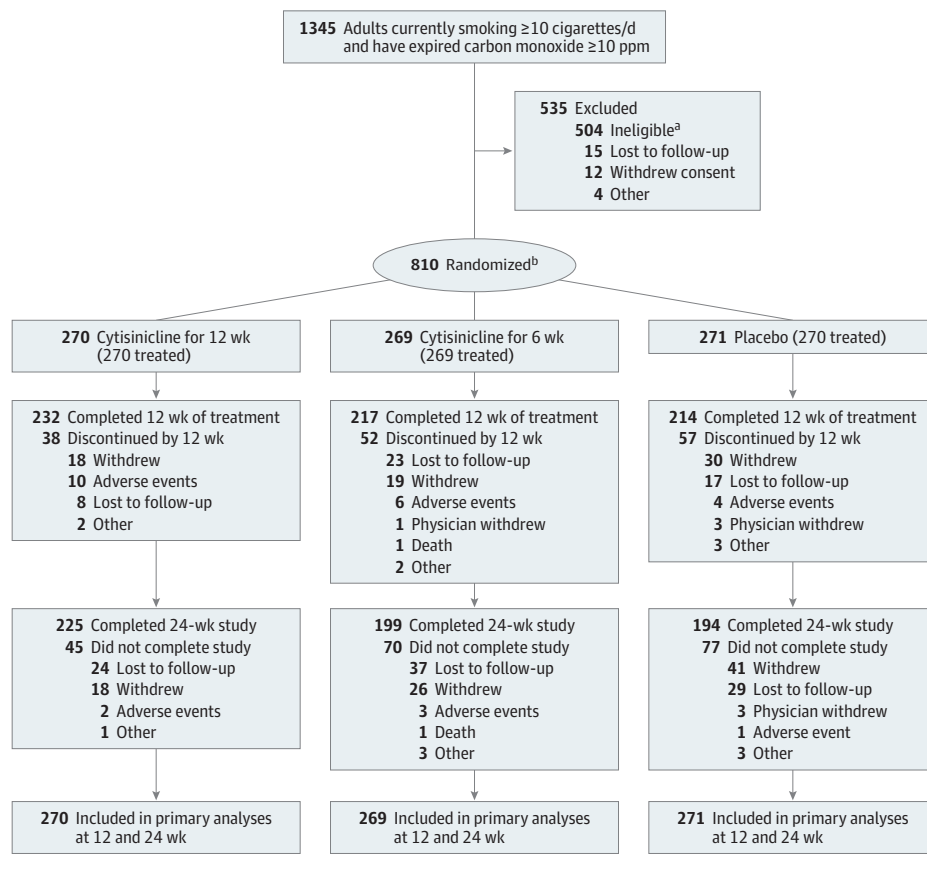
The study medication was identical-appearing tablets containing 3 mg of cytisinicline or placebo taken orally 3 times daily for 12 weeks. Participants were followed up for 12 additional weeks after treatment ended. All participants received 10 min-

utes of brief smoking cessation behavioral support provided by trained counselors at each visit for up to 15 visits from randomization through week 12. Shorter sessions were offered at weeks 16, 20, and 24.

### Assessments

Assessments after randomization were conducted at in-person visits on day 2, weekly from 1 to 12 weeks, and at weeks 16, 20, and 24. Participants who discontinued study drug prematurely were encouraged to remain in the study and complete all assessment visits. Smoking status was assessed by self-report of smoking abstinence since the last visit, measured weekly from weeks 2 through 12. A breath CO level was measured at each visit. Verified abstinence for weeks 2 to 12 required self-reported nonsmoking since the last visit and a breath CO level less than 10 ppm. Self-reported abstinence at weeks 16, 20, and 24 used the Russell Standard criteria of not

**Figure 1. Screening, Randomization, and Follow-Up of Trial Participants in the Study of Cytisinicline for Smoking Cessation in Adults Who Smoked**



smoking more than 5 cigarettes since the last visit.<sup>20</sup> Verified abstinence at 16, 20, and 24 weeks also required a breath CO level less than 10 ppm. Participants not meeting these criteria or with missing data were classified as smoking.

Safety was assessed by measurement of vital signs and participant self-report of adverse events and concomitant medications on day 2 and at weekly visits during treatment from weeks 1 to 12 and through an additional 12-week follow-up. Hematology and chemistry laboratory tests were done at weeks 1, 6, and 12. Electrocardiograms were done at weeks 6 and 12. Clinically significant adverse events or abnormalities were followed until resolution or end of study.

### Outcome Measures

The study had 2 primary end points, which assessed whether cytisnicline produced greater biochemically confirmed continuous smoking abstinence when compared with placebo during the last 4 weeks of the 6-week treatment (weeks 3 to 6) and the last 4 weeks of the 12-week treatment (weeks 9 to 12). Trial statistical success was defined as either primary end point meeting statistical criterion. Participants were allowed 1 missed visit (ie, smoking status unknown) for analysis of the primary end point. The secondary outcome measure was verified continuous smoking abstinence from the last 4 weeks of cytisnicline or placebo treatment to week 24. This outcome re-

quired verified continuous abstinence from weeks 3 to 24 for the 6-week cytisnicline treatment group and from weeks 9 to 24 for the 12-week cytisnicline group. A third secondary outcome measure compared the risk of relapse to smoking between weeks 6 and 24 among participants assigned to cytisnicline who achieved sustained abstinence during weeks 3 to 6. These individuals were either switched to placebo at week 6 or continued cytisnicline to week 12. Other prespecified end points included comparing the difference between groups in verified 7-day point-prevalence abstinence at each visit from week 2 through week 24 and assessing for evidence of effect modification for subsets defined by baseline attributes. To assess cigarette craving between groups, the Brief Questionnaire of Smoking Urges (QSU-brief) was administered at clinic visits on day 0 and at weeks 1 to 6.<sup>21,22</sup> Tolerability outcomes included the incidence of treatment-emergent serious and non-serious adverse events during treatment with cytisnicline or placebo and clinically significant changes in vital signs, laboratory tests, or electrocardiograms.

### Statistical Analysis

Analyses for the 2 binary primary and secondary outcomes were based on exact analyses  $2 \times 2$  tables that compared randomized groups, stratified by clinical site. Participants with missed assessments required for primary and secondary end

Table 2. Smoking Cessation Outcomes by Treatment Group

Outcome measure	No. (%)			Cytisinicline for 12 wk vs placebo		Cytisinicline for 6 wk vs placebo	
	Cytisinicline for 12 wk (n = 270)	Cytisinicline for 6 wk (n = 269)	Placebo (n = 271)	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value
Biochemically confirmed continuous smoking abstinence <sup>a</sup>							
Primary outcomes							
Weeks 3-6 <sup>b</sup>	60 (22.2)	68 (25.3)	12 (4.4)			8.0 (3.9-16.3)	<.001
Weeks 9-12 <sup>c</sup>	88 (32.6)	60 (22.3)	19 (7.0)	6.3 (3.7-11.6)	<.001		
Secondary outcomes <sup>d</sup>							
Weeks 3-24	32 (11.9)	24 (8.9)	7 (2.6)			3.7 (1.5-10.2)	.002
Weeks 9-24	57 (21.1)	37 (13.8)	13 (4.8)	5.3 (2.8-11.1)	<.001		

<sup>a</sup> Abstinence from cigarette smoking was defined as a self-report of no cigarettes since last visit that was confirmed by expired air carbon monoxide (co) <10 ppm. Participants with co  $\geq$ 10 ppm or missing outcome data were counted as smoking.

<sup>b</sup> Smoking abstinence reported and validated at weeks 3, 4, 5, and 6.

<sup>c</sup> Smoking abstinence reported and validated at weeks 9, 10, 11, and 12.

<sup>d</sup> Continued abstinence from cigarette smoking beyond the primary end point to week 24 was defined as a self-report of no cigarettes since last visit (through week 12 visit) or self-report of no more than 5 cigarettes since last visit at monthly visits (weeks 16, 20, and 24), with self-report confirmed by expired air co <10 ppm at each visit. Participants with co  $\geq$ 10 ppm or missing outcome data were counted as smoking.

points were classified as still smoking. A target sample of 750 participants (n = 250 per group) was computed and verified using simulations to provide 96% power for specifications of an overall 1-sided .025 type I error probability and abstinence probabilities of 7% for placebo and 19% for cytosinicline. The Hochberg procedure was used to control for primary outcome multiplicity.<sup>23</sup> Sensitivity analyses included assessments of effect modification related to subsets defined by baseline attributes using a logistic regression model. Longitudinal analyses used mixed model for repeated measures methodology with a constrained model when using prerandomization data.<sup>24</sup> Analyses of adverse events included all randomized participants who received at least 1 dose of study drug.

## Results

### Participants

Of 1345 individuals screened, 810 were eligible and randomized to 1 of 3 groups: 12 weeks of cytosinicline (n = 270), 6 weeks of cytosinicline plus 6 weeks of placebo (n = 269), or placebo (n = 271) (Figure 1). Demographic characteristics did not differ between screened individuals who were randomized or not randomized. Primary efficacy analyses included all 810 randomized participants. Analyses of adverse events (n = 809) excluded 1 participant in the placebo group who received no study medication. Follow-up visits ended in December 2021.

Individuals in all groups were comparable on baseline characteristics, including age, sex, race and ethnicity, smoking and quitting history, nicotine dependence,<sup>17</sup> and anxiety and depression symptoms (Table 1). Participants smoked a mean of 19.4 cigarettes per day. Overall, 663 participants (81.9%) completed 12 weeks of study drug treatment (12-week cytosinicline group: 232 [85.9%], 6-week cytosinicline group: 217 [80.7%], placebo group: 214 [79.0%]). Study drug

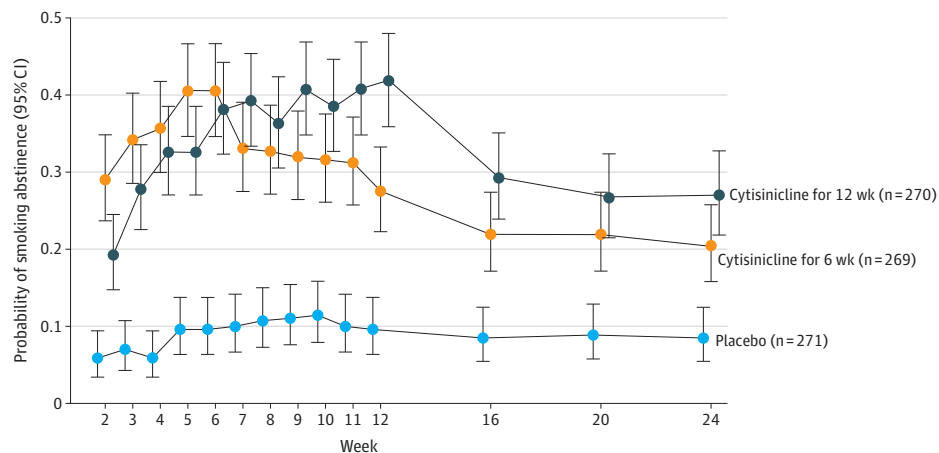
compliance was high: 79.3% of participants in the 12-week cytosinicline group, 76.6% in the 6-week cytosinicline group, and 69.3% in the placebo group took 90% or more of the study drug doses. Compliance with behavioral support was also high, with 92.8% of planned sessions completed by participants in the 12-week cytosinicline group, 89.5% in the 6-week cytosinicline group, and 86.8% in the placebo group. Follow-up assessments were completed by 618 participants (76.3%) at 24 weeks (12-week cytosinicline group: 225 [83.3%], 6-week cytosinicline group: 199 [74.0%], and placebo group: 194 [71.6%]). Participants who did and did not complete follow-up did not differ significantly in age, sex, or number of cigarettes smoked per day at baseline.

### Efficacy

Biochemically confirmed continuous smoking abstinence during the last 4 weeks of treatment, the primary outcome measure, was significantly higher for cytosinicline compared with placebo at both treatment durations (Table 2). For 6-week cytosinicline treatment vs placebo, 25.3% vs 4.4% of participants were abstinent during weeks 3 to 6 (odds ratio [OR], 8.0 [95% CI, 3.9-16.3];  $P < .001$ ). For 12-week cytosinicline treatment vs placebo, the difference was 32.6% vs 7.0% during weeks 9 to 12 (OR, 6.3 [95% CI, 3.7-11.6];  $P < .001$ ).

Continuous abstinence from the last 4 weeks of treatment through 6 months (secondary outcome measure) was significantly higher at both cytosinicline treatment durations vs placebo (Table 2). For 6-week cytosinicline treatment vs placebo, 8.9% vs 2.6% of participants were abstinent during weeks 3 to 24 (OR, 3.7 [95% CI, 1.5-10.2];  $P = .002$ ). For 12-week cytosinicline treatment vs placebo, 21.1% vs 4.8% of participants were abstinent during weeks 9 to 24 (OR, 5.3 [95% CI, 2.8-11.1];  $P < .001$ ). eTable 1 in Supplement 3 provides relative risk and number needed to treat estimates based on exact analysis of the 2  $\times$  2 table of group by binary

Figure 2. Weekly Prevalence Probabilities of Biochemically Confirmed Tobacco Abstinence by Group



At each week, participants reported whether cigarettes were smoked in the last 7 days. A participant was classified as abstinent for that week if no smoking was reported and was biochemically confirmed. Missing assessments were classified as nonabstinence in order to include all randomized. The prevalence probabilities and exact 95% CIs were estimated at each week.

outcome (unstratified because no evidence suggested clinical site effect modification). Confidence intervals were computed algebraically from exact ORs and 95% CIs.<sup>25</sup>

Among participants who were assigned to either cytosinicline group and who achieved continuous abstinence during weeks 3 to 6, the individuals who continued cytosinicline for an additional 6 weeks (12-week cytosinicline group) did not have a significantly different rate of relapse-free abstinence during weeks 6 to 24 compared with individuals in the 6-week cytosinicline group who switched to placebo at week 6 (10.4% vs 13.3%; OR, 1.31 [95% CI, 0.75-2.33];  $P = .35$ ). For this analysis, individuals who were not abstinent at weeks 3 to 6, 12, 16, 20, and 24 were regarded as having relapsed.

Figure 2 displays the weekly estimated prevalence probabilities of being abstinent. A participant who reported no cigarettes smoked in the last 7 days and provided biochemical confirmation was classified as abstinent. Both cytosinicline groups illustrated progressively increasing probabilities of abstinence over the first 6 weeks of treatment and had clinically meaningful higher probabilities than placebo throughout active treatment. The estimated ORs with 95% CIs for comparisons with placebo at every week, and in particular for the posttreatment follow-up weeks, did not include 1 (Figure 2).

Assessment of heterogeneity of subsets defined by baseline attributes are shown in eFigure 2 in Supplement 3. No evidence of effect modification was evident for the subgroups defined by age, sex, or number of cigarettes smoked per day.

The mean total cigarette craving score, using the QSU-brief, declined more rapidly between baseline and week 6 among participants who received cytosinicline for 6 or 12 weeks compared with placebo (eFigure 3 in Supplement 3). Confidence intervals for the effect estimates at weeks 1 to 6 excluded 0, providing evidence of a rapid and sustained effect.

### Safety

Treatment-emergent adverse events were reported by 184 participants (68.2%) in the 12-week cytosinicline group, 172 (63.9%) in the 6-week cytosinicline group, and 166 (61.5%) in the placebo

group (Table 3). The majority of adverse events were non-serious and mild to moderate in severity. Across all 3 groups, nausea, headache, abnormal dreams, and insomnia were the most common (>5%) adverse events, but only the incidences of abnormal dreams and insomnia were higher in the cytosinicline groups compared with placebo. Study drug discontinuation due to adverse events occurred in 16 (2.9%) of 539 participants receiving cytosinicline (6-week group: 2.2%, 12-week group: 3.7%), and 4 (1.5%) of 270 participants receiving placebo (Figure 1). Serious adverse events occurred in 18 (3.3%) of 539 participants who received cytosinicline and in 3 (1.1%) of 270 participants who received placebo (OR, 3.08 [95% CI, 0.98-13.18]) (Table 3). No serious adverse event was judged to be treatment-related, including the 1 death that occurred in the 6-week cytosinicline group.

### Discussion

This multisite, placebo-controlled, phase 3, randomized clinical trial tested the efficacy and tolerability of a novel regimen of cytosinicline. Both 6- and 12-week schedules administered cytosinicline at a dose of 3 mg taken 3 times daily, combined with behavioral support, and both demonstrated robust efficacy for smoking cessation among adults who sought to quit smoking. Participants in the cytosinicline groups had 6- to 8-fold higher odds of continuous smoking abstinence at the end of treatment than participants receiving placebo plus behavioral support. The efficacy of cytosinicline treatment for both 6 and 12 weeks, compared with placebo, was sustained to 24-week follow-up and was consistently demonstrated in subgroups defined by baseline characteristics. At 24 weeks, this new regimen produced 1 additional person abstinent for every 6 people treated with cytosinicline for 12 weeks or for every 11 people treated for 6 weeks (eTable 1 in Supplement 3). Cytosinicline reduced nicotine craving and was well tolerated by participants, who adhered to the treatment schedule at a high rate, even though the trial was conducted during the early phases of the US COVID-19 pandemic.

Table 3. Summary of Adverse Events by Treatment Group<sup>a</sup>

Outcome measure	No. (%)		
	Cytisinicline for 12 wk (n = 270)	Cytisinicline for 6 wk (n = 269)	Placebo (n = 270) <sup>a</sup>
No. of participants with			
Any treatment-emergent adverse event	184 (68)	172 (64)	166 (62)
Any serious adverse event <sup>b</sup>	8 (3)	10 (4)	3 (1)
Any treatment-related serious adverse event <sup>c</sup>	0	0	0
No. of treatment emergent adverse events			
Mild	303 (61)	290 (63)	239 (67)
Moderate	178 (36)	148 (32)	114 (32)
Severe	13 (3)	21 (5)	6 (2)
Most frequent treatment-emergent adverse events <sup>d</sup>			
Insomnia	26 (10)	23 (9)	13 (5)
Abnormal dreams	21 (8)	22 (8)	8 (3)
Headache	21 (8)	18 (7)	22 (8)
Nausea	15 (6)	16 (6)	20 (7)
Constipation	13 (5)	16 (6)	3 (1)
Anxiety	15 (6)	7 (3)	5 (2)
Diarrhea	12 (4)	10 (4)	15 (6)

<sup>a</sup> Analysis limited to participants who took at least 1 dose of study medication. Because 1 participant randomized to the placebo group (n = 271) took no study medication, the denominator for this analysis is 270).

<sup>b</sup> Serious adverse event was defined as an adverse event that resulted in death or was life-threatening; required hospitalization or prolonged an existing hospitalization; resulted in persistent or significant disability, incapacity, or congenital abnormality; or which required medical intervention to prevent any of the above outcomes.

<sup>c</sup> A serious adverse event's relationship to treatment was judged by responsible

investigator using best medical judgment and based on a reasonable temporal sequence from the time of study drug administration, and/or a known response pattern to the study drug; could not have been produced by other factors such as the participant's clinical state, therapeutic intervention, or concomitant therapy; and either occurred immediately following study drug administration or improved on stopping the study drug.

<sup>d</sup> Includes all treatment-emergent adverse events reported by 5% or more of participants in any study group. Listed in descending order by combined cytisinicline for 6 and 12 weeks.

Among cytisinicline-treated participants who achieved 4 weeks of tobacco abstinence by week 6, an additional 6 weeks of cytisinicline treatment, compared with stopping at week 6, did not lower a participant's risk of relapse (ie, resuming smoking during weeks 6 to 24). However, point-prevalence abstinence rates in the group treated with cytisinicline for 12 weeks continued to increase after week 6 (Figure 2), suggesting that quitting continued to occur among participants who did not attain abstinence by week 6 and continued to receive cytisinicline. This appears to have contributed to those in the 12-week cytisinicline group achieving successful abstinence at weeks 9 to 12 compared with placebo. The observation that some participants who did not quit smoking when treatment started but achieved abstinence later during a period of ongoing treatment has also been reported with varenicline, which has pharmacological properties similar to cytisinicline, but it has not been observed with other smoking cessation pharmacotherapies.<sup>26,27</sup>

The effect size and absolute level of tobacco abstinence achieved with cytisinicline at 6-month follow-up in this trial were larger than the continuous 6-month abstinence rate in a previous placebo-controlled trial that used the drug's traditional dosing and in a recent systematic review of cytisinicline clinical trials.<sup>11,28</sup> This supports the hypothesis that a higher dose and longer treatment duration increases cytisinicline's efficacy while maintaining acceptable tolerability.

Indirect support also comes from an open-label, randomized trial of people who smoked and underwent lung cancer screening.<sup>29</sup> In that trial, cytisinicline given for 40 or 84 days, plus smoking cessation counseling, was more effective than counseling alone, with 12-month verified continuous abstinence rates and adjusted ORs exceeding those achieved in the prior 25-day trial.<sup>11,29</sup>

Cytisinicline was directly compared with varenicline in 2 noninferiority trials. It was noninferior to varenicline for smoking cessation in the trial that included a cytisinicline maintenance dose through 12 weeks, but it failed to show noninferiority to varenicline in a trial that compared cytisinicline taken for 25 days vs varenicline taken for 84 days.<sup>13,30</sup> In both trials, participants reported significantly fewer adverse events with cytisinicline than with varenicline. Cytisinicline administered for 25 days outperformed a nicotine patch used for 8 weeks in the 1 published trial directly comparing these drugs.<sup>12</sup> That trial used a lower dose and shorter duration of cytisinicline than was tested in the current trial.

### Limitations

This study had several limitations. First, it enrolled a predominantly White sample, limiting generalizability for other racial and ethnic groups. Second, it excluded participants with a diagnosis of serious mental illness, suicidal ideation, moderate to severe depression symptoms, recent unstable cardiovascular

disease, and current marijuana or illicit drug use, limiting the generalizability of the findings to these groups. Third, adverse event reports were assessed for 24 weeks, but the trial was not large enough or long enough to detect uncommon adverse events. However, cytidinicline has been used for decades as a cessation aid by millions of people who smoke in Central and Eastern Europe and the 25-day regimen has a good safety record.<sup>9</sup> Fourth, while participants were followed up for at least 12 weeks after study drug treatment ended, a longer durability of posttreatment abstinence cannot be ascertained from the trial. Fifth, the intensity of behavioral support and atten-

tion to treatment dosing in this trial likely exceeds what can be provided in typical health care settings.

## Conclusions

This phase 3, multisite, placebo-controlled, randomized clinical trial, the first large trial conducted in the US, demonstrated that a novel regimen of cytidinicline, along with behavioral support, has robust efficacy and excellent tolerability as a treatment for tobacco dependence.

### ARTICLE INFORMATION

**Accepted for Publication:** May 23, 2023.

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**Author Contributions:** Drs Rigotti and Blumenstein 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.

**Concept and design:** All authors.

**Acquisition, analysis, or interpretation of data:**

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**Drafting of the manuscript:** Rigotti, Leischow, Nides, Blumenstein, Clarke, Cain, Jacobs.

**Critical revision of the manuscript for important intellectual content:** Rigotti, Benowitz, Prochaska, Leischow, Clarke, Cain, Jacobs.

**Statistical analysis:** Blumenstein, Jacobs.

**Obtained funding:** Cain, Jacobs.

**Administrative, technical, or material support:**

Leischow, Cain.

**Supervision:** Rigotti, Prochaska, Leischow, Clarke, Jacobs.

**Other-regulatory coordination with FDA for conducting this trial:** Jacobs.

**Conflict of Interest Disclosures:** Dr Rigotti reported receiving grants and personal fees from Achieve Life Sciences during the conduct of the study; personal fees from UpToDate outside the submitted work; and funds from the National Cancer Institute, paid through contracts with Bizzell US and Strategix Management LLC, to co-chair the workshop, Current State of Tobacco Cessation Interventions and Tobacco Prevention Research. Dr Benowitz reported receiving personal fees for serving on a data monitoring board for Achieve Life Sciences during the conduct of the study and personal fees from being an expert witness against tobacco companies outside the submitted work. Dr Prochaska reported receiving personal fees for serving on a data monitoring board for Achieve Life Sciences during the conduct of the study and personal fees from plaintiff law firms in litigation

against tobacco companies for expert witness work and from technology companies developing treatments for quitting smoking for consulting and advising outside the submitted work. Dr Leischow reported receiving grants from Achieve Life Sciences during the conduct of the study and nonfinancial support from Pfizer (medication for a National Institutes of Health-funded study on over-the-counter use of varenicline) outside the submitted work. Dr Nides reported receiving personal fees from Achieve Life Sciences during the conduct of the study and personal fees from Pfizer outside the submitted work. Dr Blumenstein reported being a self-employed biostatistical consultant to Achieve Life Sciences. Dr Clarke reported being an employee of Achieve Life Sciences; in addition, Dr Clarke had a patent for succinate salt of cytidine and use thereof issued and a patent for compositions comprising cytidine in the treatment and/or prevention of addiction in subjects in need thereof pending. Mr Cain reported being an employee of Achieve Life Sciences; in addition, Mr Cain had patents 11083715 and 11083716 issued to Achieve Life Sciences. Dr Jacobs reported being an employee of Achieve Life Sciences; in addition, Dr Jacobs had patents 11083715 and 11083716 issued to Achieve Life Sciences.

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**Data Sharing Statement:** See Supplement 4.

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## Supplemental Online Content

Rigotti NA, Benowitz NL, Prochaska J, et al. Cytisinicline for smoking cessation: a randomized clinical trial. *JAMA*. doi:10.1001/jama.2023.10042

**eFigure 1.** ORCA-2 Study Design

**eFigure 2.** Continuous Abstinence at End of Treatment: Effect Modification

**eFigure 3.** Total Score of Brief Questionnaire of Smoking Urges Over Time, by Group

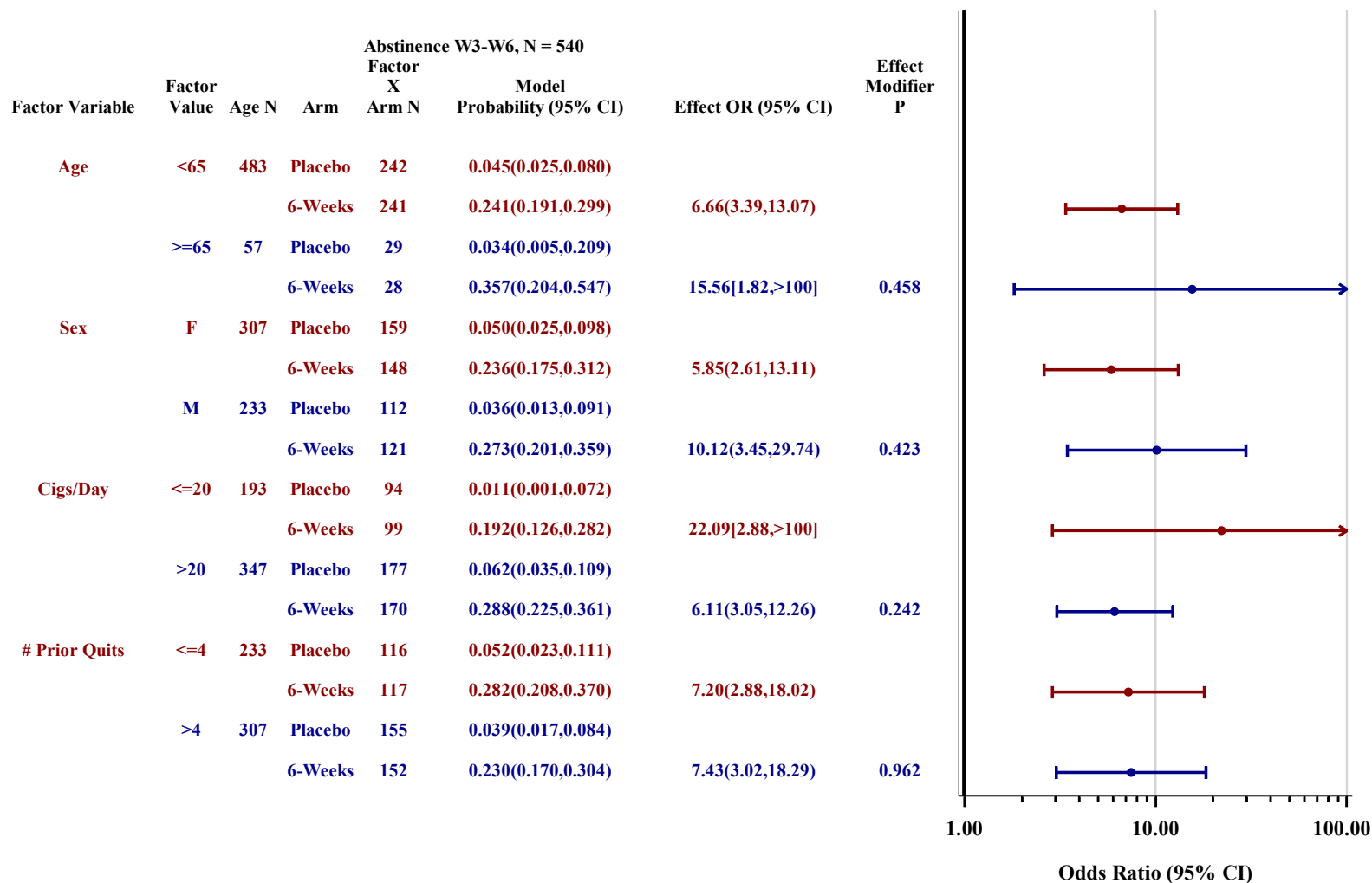
**eTable.** Biochemically Confirmed Continuous Smoking Abstinence by Arm

This supplemental material has been provided by the authors to give readers additional information about their work.

**eFigure 1. ORCA-2 Study Design**

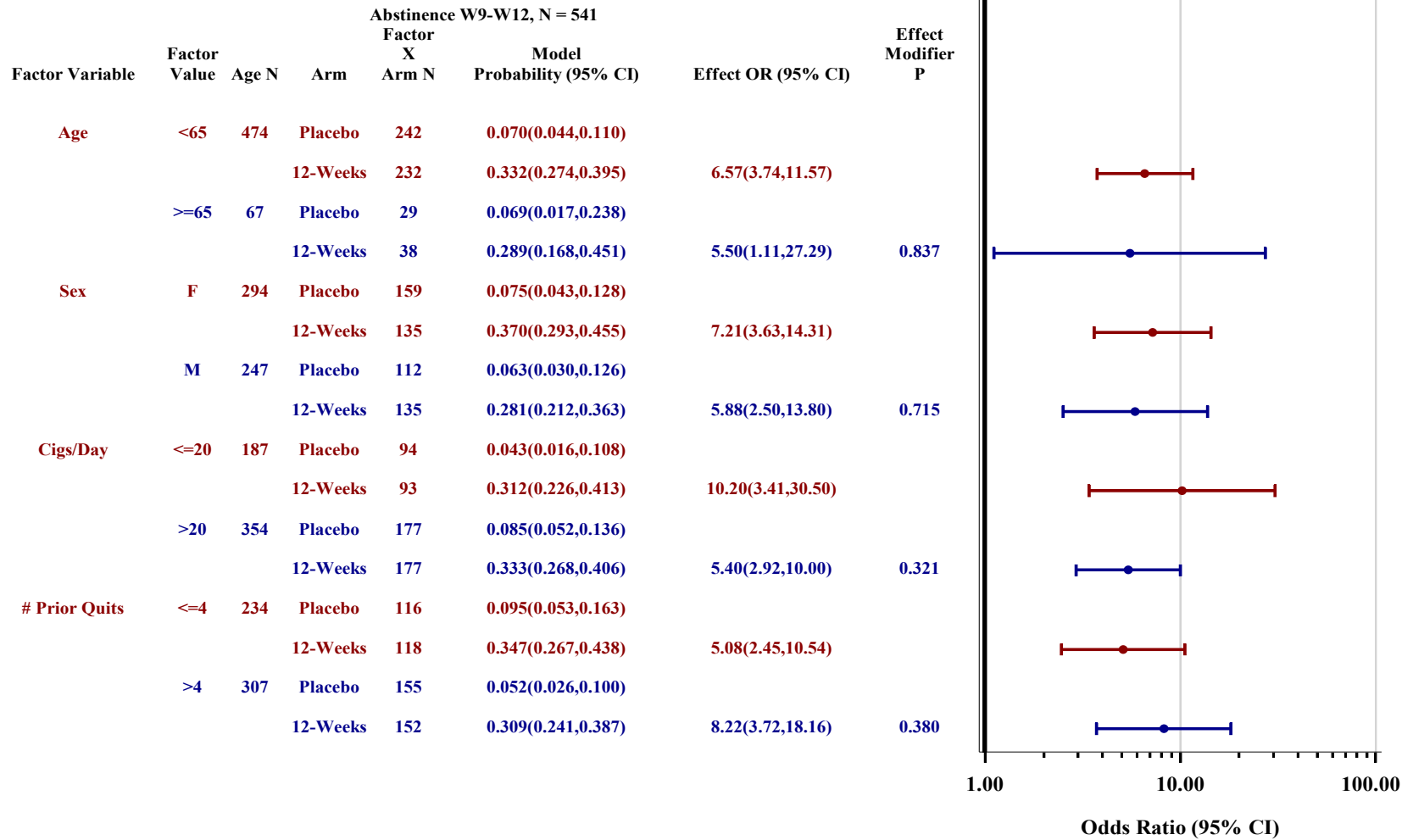


**eFigure 2: Continuous Abstinence at End of Treatment: Effect modification**



**Panel A**

OR = Odds ratio = odds (experimental)/odds (control). CI = confidence interval. EMA = Effect Modifier Analysis (a small P suggests group OR heterogeneity).

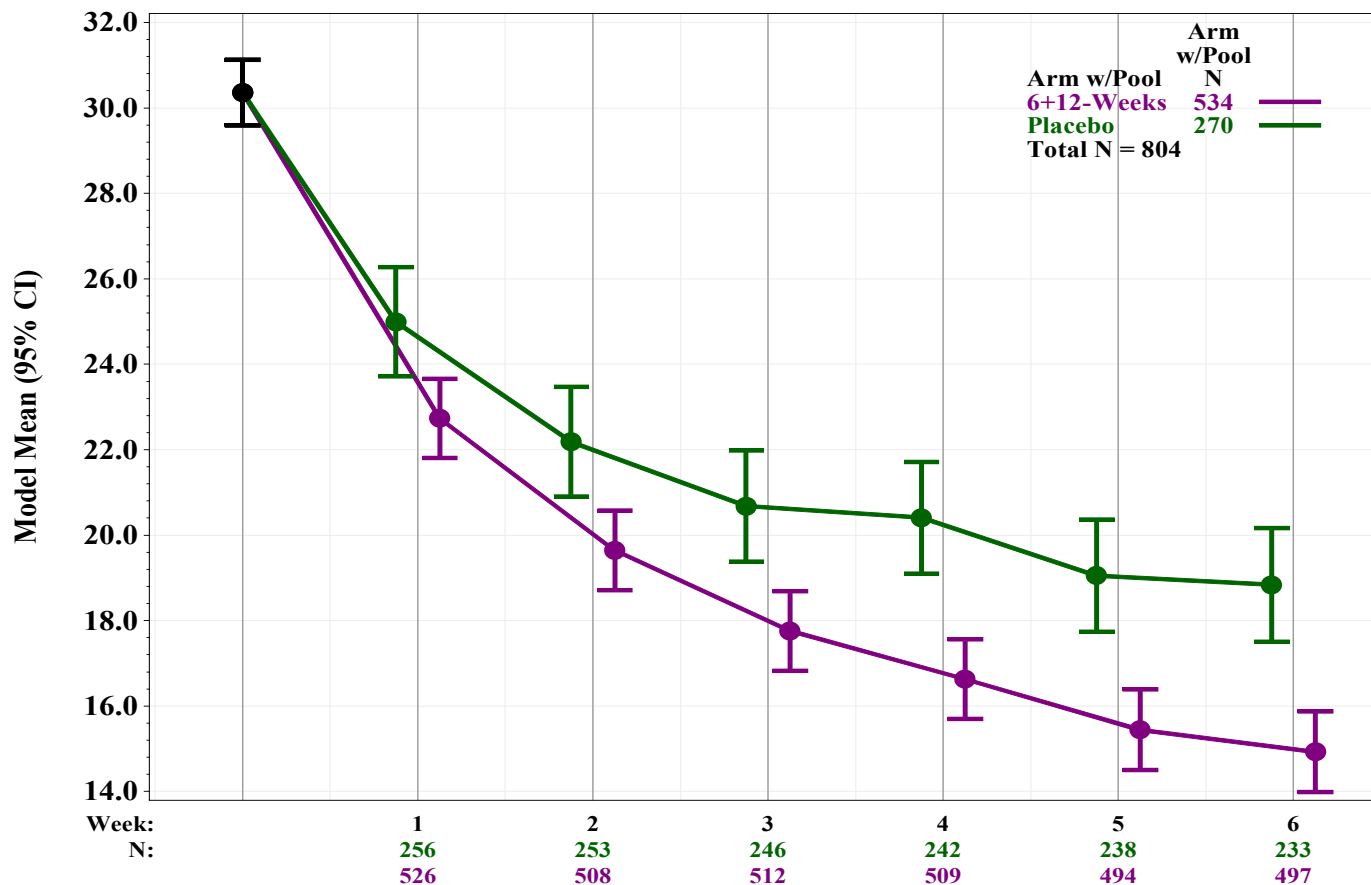


### Panel B

OR = Odds ratio = odds (experimental)/odds (control). CI = confidence interval. EMA = Effect Modifier Analysis (a small P suggests group OR heterogeneity).

Forest graphs provide results of effect modification analyses (EMAs) for the two primary endpoints, abstinence from weeks 3 to 6 (Panel A) and from weeks 9 to 12 (Panel B). The results are shown for selected baseline factors of particular interest. For each factor, the group effect odds ratio (OR) is estimated for each subset defined by the factor using logistic regression of the analysis variable with terms for group, factor, and group-by-factor interaction. Evidence of effect modification is a departure from group effect homogeneity across factor categories. The departure from homogeneity is indicated when the effect-by-factor interaction P value is small, with  $\leq .10$  as the usual criterion for small. These EMAs and EMAs for other baseline attributes not shown failed to find material suggestions of effect modification. These EMAs are exploratory and there is no adjustment for multiplicity.

eFigure 3: Total Score of Brief Questionnaire of Smoking Urges Over Time, by Group



During the first 6 weeks of treatment, mean cigarette craving score, as measured by the Brief Questionnaire of Smoking Urges (QSU-brief), declined more among patients randomized to the pooled cytisinicline arms for 6 weeks or 12 weeks than compared to those randomized to placebo. Mixed Model Repeated Measures (MMRM) with unstructured covariance and with baseline as a repeated measure was used to estimate the mean at each visit.<sup>23</sup> The 95% confidence intervals for the mean estimates are shown at all visits.

**eTable. Biochemically Confirmed Continuous Smoking Abstinence<sup>a</sup> by Arm: Relative Risk and Risk Difference**

	Duration of Continuous Smoking Abstinence <sup>a</sup>	Placebo (Arm A) N=271		Cytisinicline 6 weeks (Arm B) N=269		Cytisinicline 12 weeks (Arm C) N=270		Cytisinicline–6 weeks vs. placebo (Arm B vs. Arm A)			Cytisinicline–12weeks vs. placebo (Arm C vs. Arm A)		
		Abstinent		Abstinent		Abstinent		Relative Risk (95% CI)	Risk Difference (95% CI)	NNT <sup>e</sup> (95% CI)	Relative Risk (95% CI)	Risk Difference (95% CI)	NNT <sup>e</sup> (95% CI)
		n	%	n	%	n	%						
<b>Primary Outcomes</b>	Weeks 3-6 <sup>b</sup>	12	4.4	68	25.3	60	22.2	5.71 (3.26,10.74)	0.21 (0.16,0.25)	5 (4,7)	5.02 (2.84,9.50)	0.18 (0.13,0.22)	6 (4,8)
	Weeks 9-12 <sup>c</sup>	19	7.0	60	22.3	88	32.6	3.18 (1.98,5.30)	0.15 (0.10,0.20)	7 (4,11)	4.65 (2.98,7.58)	0.26 (0.20,0.30)	4 (3,6)
<b>Secondary Outcomes</b>	Weeks 3-24 <sup>d</sup>	7	2.6	24	8.9	32	11.9	3.45 (1.56,8.50)	0.06 (0.03,0.09)	16 (10,40)	4.59 (2.15,11.05)	0.09 (0.05,0.12)	11 (8,20)
	Weeks 9-24 <sup>d</sup>	13	4.8	37	13.8	57	21.1	2.87 (1.59,5.46)	0.09 (0.04,0.13)	11 (7,24)	4.40 (2.53,8.15)	0.16 (0.11,0.20)	6 (4,9)

<sup>a</sup>Abstinence from cigarette smoking is defined as a self-report of no cigarettes since last visit that is confirmed by expired air CO <10 ppm.

Participants with CO<sub>≥</sub>10 or missing outcome data are counted as smokers.

<sup>b</sup> Smoking abstinence reported and validated at weeks 3, 4, 5, and 6.

<sup>c</sup> Smoking abstinence reported and validated at weeks 9, 10, 11, and 12.

<sup>d</sup> Continued abstinence from cigarette smoking beyond the primary endpoint to Week 24 is defined as a self-report of no cigarettes since last visit (through week 12 visit) or self-report of no more than 5 cigarettes since last visit at monthly visits (weeks 16, 20, and 24), with self-report confirmed by expired air CO <10 ppm at each visit. Participants with CO<sub>≥</sub>10 or missing outcome data are counted as smokers.

<sup>e</sup> NNT=Number needed to treat (rounded to integers)