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Efficacy of cytisinicline for smoking cessation in adults with and without multiple prior quit attempts or prior pharmacotherapy use: Pooled analysis of two phase 3 trials

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Off-label medication uses discussed:	Cytisinicline is a partial agonist/antagonist with selective binding affinity for nicotine receptors and is under investigation for the treatment of nicotine dependence for smoking cessation in adults.		
Industry funding to the investigator in the last 5 years; list all	**NAR** has received grant funding from Achieve Life Sciences. **MLR** is an employee and owns stock/stock options in Achieve Life Sciences. **NLB** has reported personal fees from Achieve Life Sciences for data safety monitoring board membership, personal fees from Qnovia for advisory board membership, and serving as an expert witness in litigation against tobacco companies. **CJ** was an employee at Achieve Life Sciences at the time the current analysis was performed and owns stock/stock options in the company. **JJP** has reported acting as a data and safety monitoring board adviser to Achieve Life Sciences, serving as an advisory board member at OneLeaf, and serving as an expert witness in litigation against tobacco companies.		
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Introduction

- Cytisinicline is a partial agonist at α4β2 nicotinic acetylcholine receptors[1,2]
- Two phase 3 randomized clinical trials (ORCA-2, ORCA-3) of adults seeking to quit smoking demonstrated the efficacy of cytisinicline for smoking cessation and a favorable safety profile[1,2]
- Many people trying to quit smoking have made multiple attempts and previously used FDA-approved medications

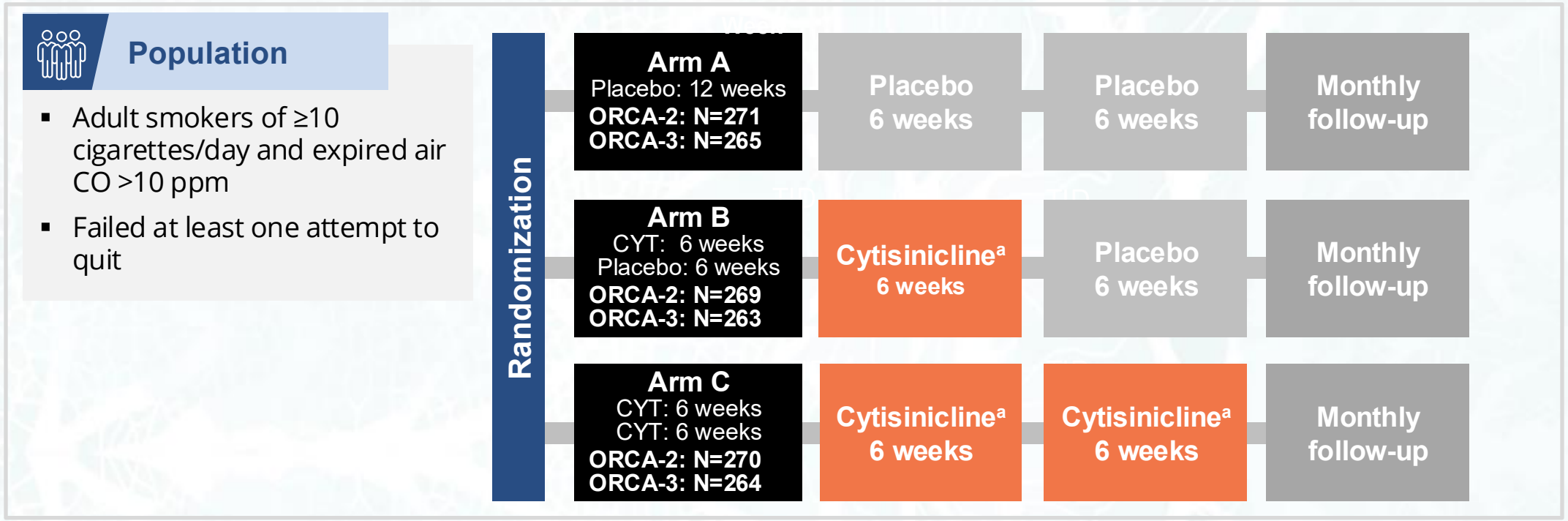
Understanding cytisinicline's efficacy in individuals who previously used current FDA-approved medications will aid clinical decision-making

1. Rigotti NA et al. JAMA. 2023;330:152–60; 2. Rigotti NA et al. JAMA Intern Med. 2025;185:648–55.
Food and Drug Administration; ORCA, Ongoing Research of Cytisinicline for Addiction.

Study question

How does the use of prior smoking cessation medications or a history of multiple failed quit attempts affect the efficacy and tolerability of cytisinicline?

Study design: Pooled ORCA-2 and ORCA-3 populations[1,2]



1. Rigotti NA et al. JAMA. 2023;330:152–60; 2. Rigotti NA et al. JAMA Intern Med. 2025;185:648–55.
[a]Participants received cytisinicline 3 mg TID.
CO, carbon monoxide; CYT, cytisinicline; ppm, parts per million; cytisinicline was administered three times daily.

Methods: Endpoints

Efficacy endpoints

- **Primary endpoint:** Biochemically verified smoking abstinence[a] during the last 4 weeks of treatment in the 6-week or 12-week treatment groups
- **Secondary endpoint:** Biochemically verified continued smoking abstinence from the last 4 weeks of treatment to Week 24

Safety endpoint

- Treatment-emergent adverse events (TEAEs)

1. West R et al. Addiction. 2005;100:299–303.
[a]Self-reported abstinence (≤5 cigarettes) since the last visit and a breath CO level <10 ppm.[1]
CO, carbon monoxide; TEAE, treatment-emergent adverse event.

Methods: Subgroups and statistics

Subgroups

Prior use of:

- Varenicline
- Bupropion
- Nicotine replacement therapy (NRT)

Prior quit attempts:

- ≤4 past quit attempts
- >4 past quit attempts

Statistics[a]

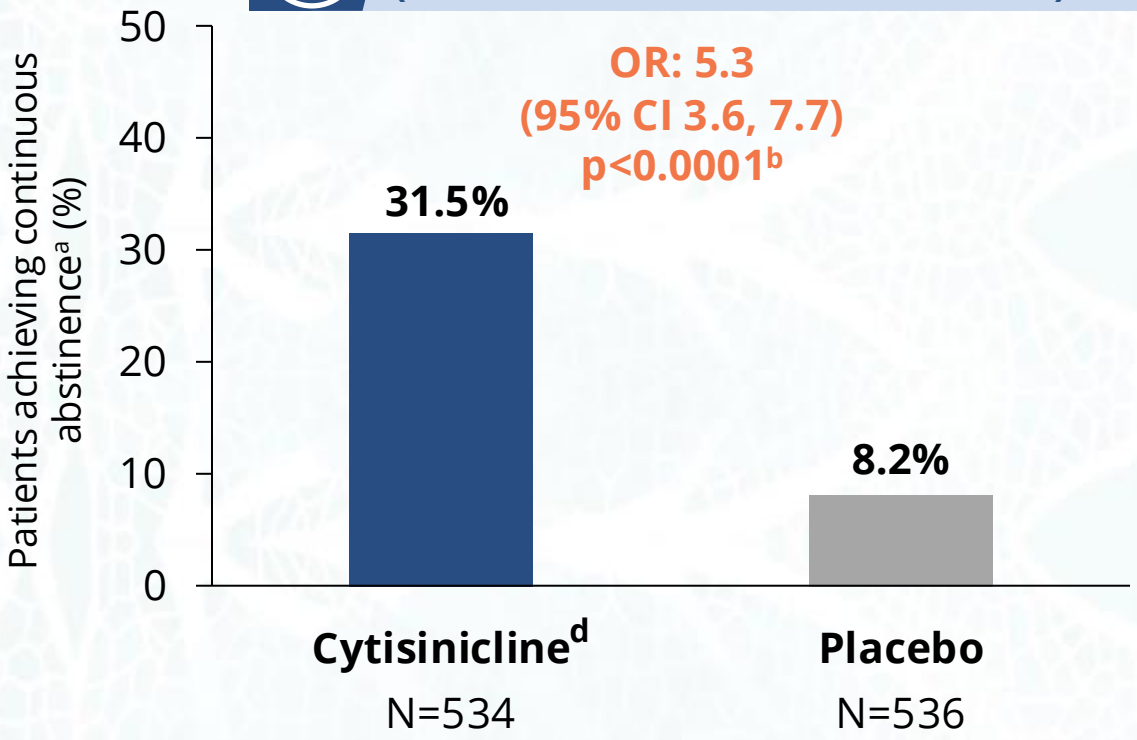
- Odds ratio computed from a logistic regression model adjusted for age, sex, smoking duration, and number of prior quit attempts[b,c]
- Two-sided p-value for the interaction between the treatment effect and subgroup factor was derived from a logistic regression model with additional interaction term

[a]For baseline characteristic data, two-sided p-values were computed using Fisher's exact test or chi-square test for categorical variables and an F-test for numeric variables;
[b]The last covariate was removed from the model in the subgroup analysis by the number of prior quit attempts;
[c]Two-sided p-value for the treatment effect was derived from the same logistic regression model.
NRT, nicotine replacement therapy.

Results: Smoking abstinence for 12-week treatment

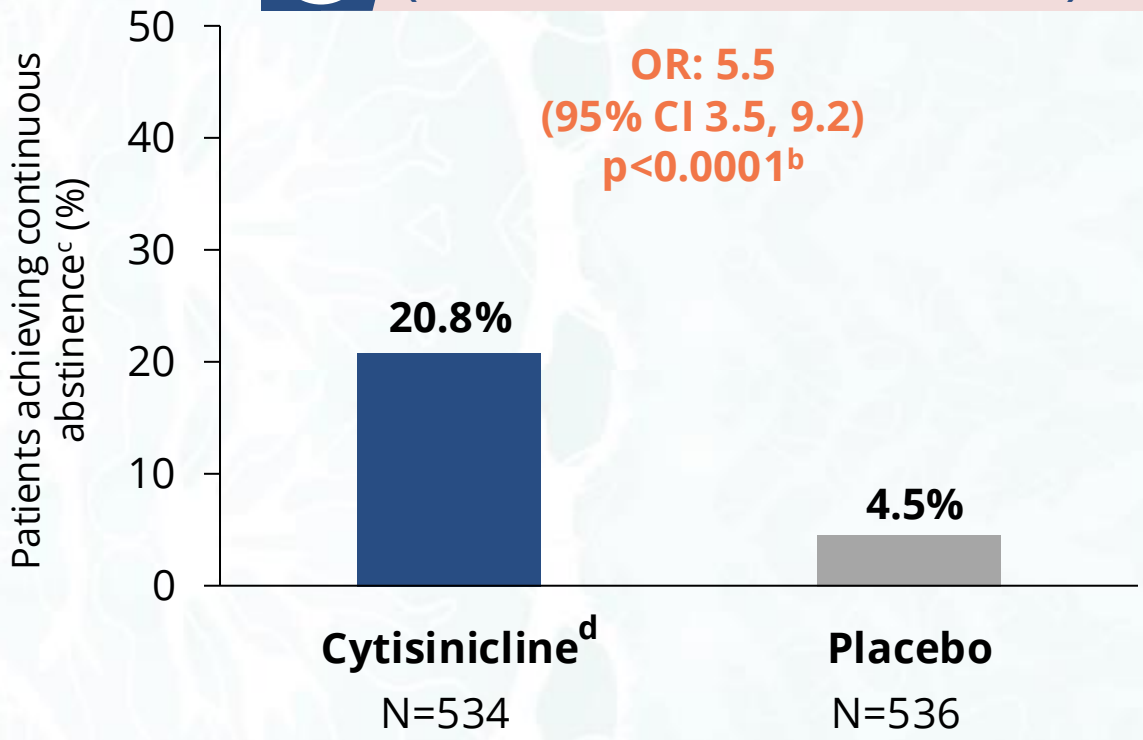
Primary endpoint

9–12 Cytisinicline 12 weeks pooled (continuous abstinence Weeks 9–12)



Secondary endpoint

9–24 Cytisinicline 12 weeks pooled (continuous abstinence Weeks 9–24)



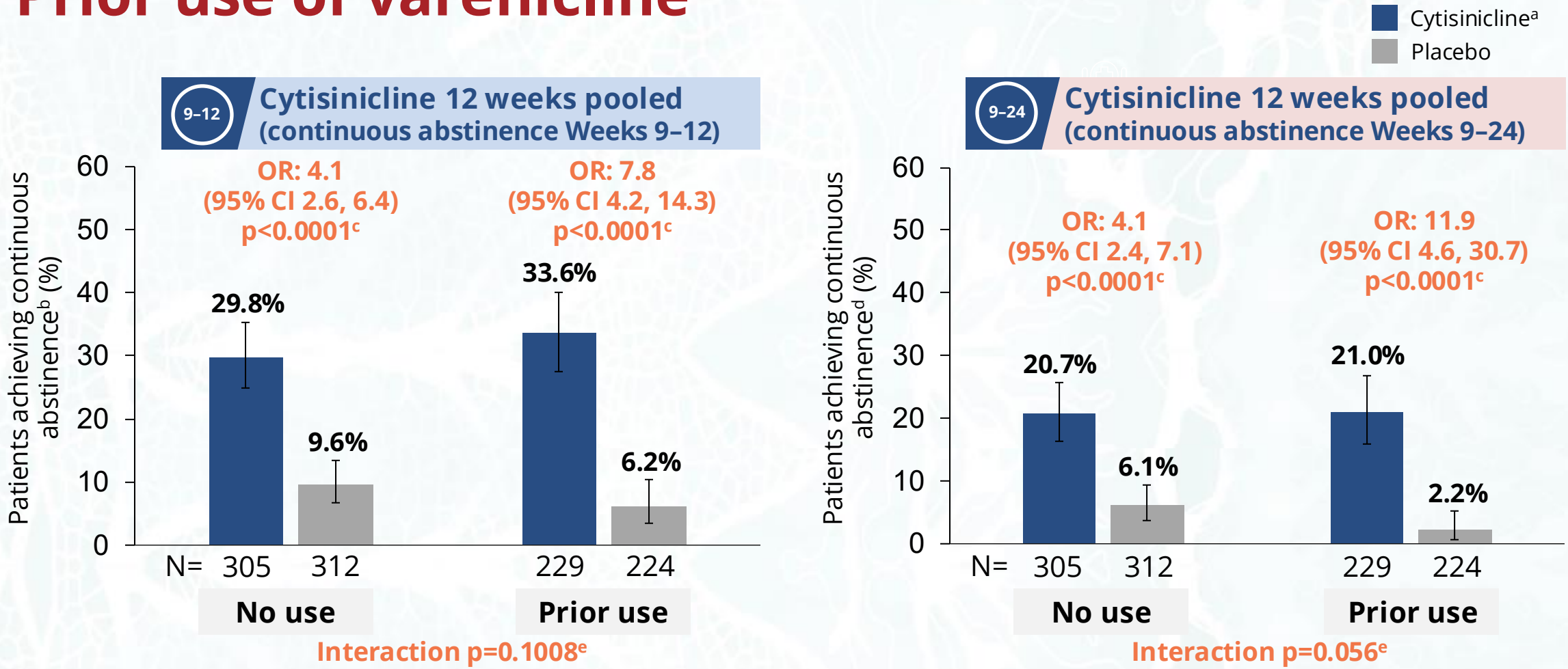
[a]Participants who achieved 4 weeks of continuous CO-verified smoking abstinence from Week 9 to Week 12; [b]P-value for differences in proportion, via Cochran-Mantel-Haenszel test; [c]Participants who achieved continuous CO-verified smoking abstinence from Week 9 to Week 24; [d]Participants received cytisinicline 3 mg TID.
CI, confidence interval; CO, carbon monoxide; OR, odds ratio; TID, three times daily.

Baseline characteristics by prior medication use

Characteristic	Varenicline		Bupropion		NRT	
	No use (N=931)	Prior use (N=671)	No use (N=1279)	Prior use (N=323)	No use (N=1147)	Prior use (N=455)
Sex, n (%) Female	**476 (51.1)**	**405 (60.4)**	**666 (52.1)**	**215 (66.6)**	**609 (53.1)**	**272 (59.8)**
Age, years Median (Min, Max)	**51 (18, 84)**	**56 (29, 84)**	**53 (18, 84)**	**56 (30, 83)**	53 (18, 84)	54 (21, 82)
Smoking duration, years Mean (SD)	**33.4 (13.4)**	**39.1 (11.4)**	**34.9 (13.1)**	**39.4 (11.7)**	35.9 (12.8)	35.7 (13.2)
Number of cigarettes/day in past 30 days Median	20	20	20	20	20	20
Fagerstrom test of nicotine dependence Mean (SD)	5.6 (1.8)	5.7 (1.8)	5.6 (1.8)	5.8 (1.7)	5.6 (1.8)	5.6 (1.8)

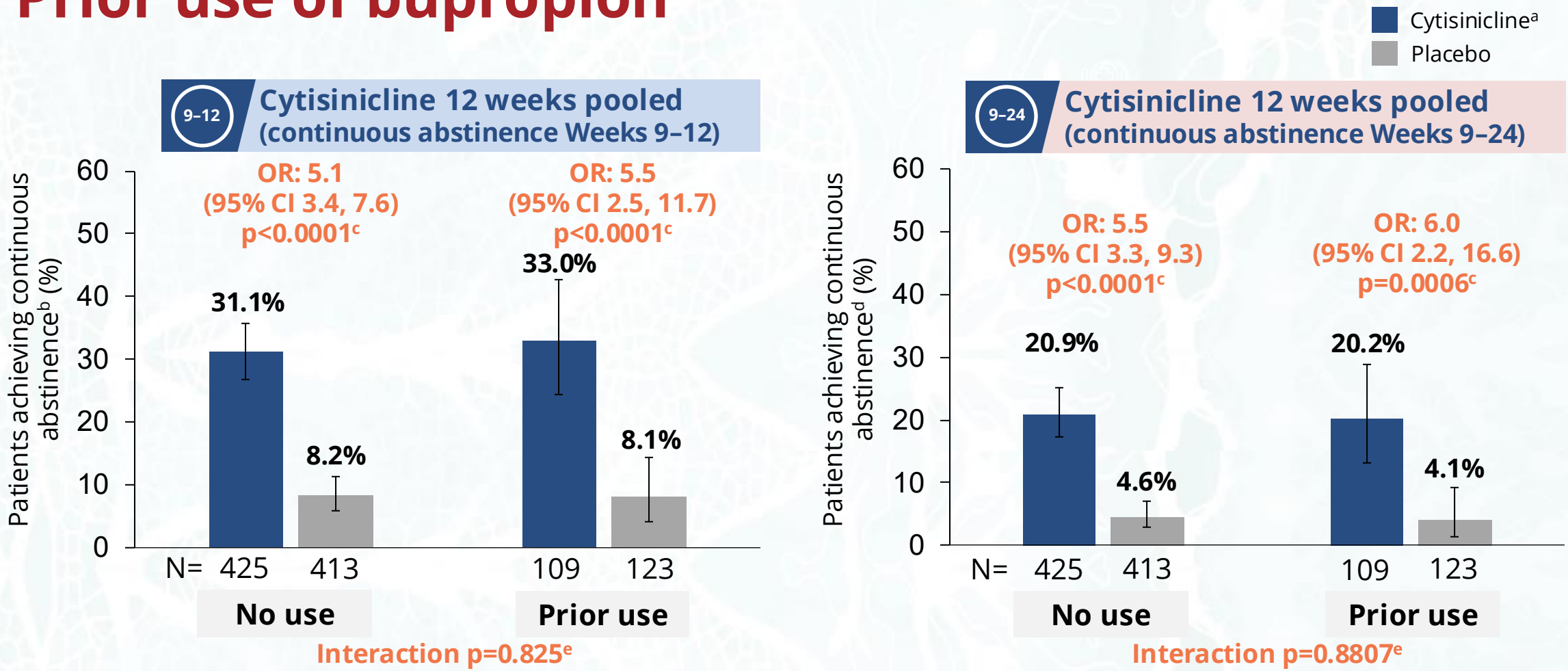
Two-sided p-value and an F-test for numeric variables; bold for $p<0.05$.
NRT, nicotine replacement therapy; SD, standard deviation.

Prior use of varenicline



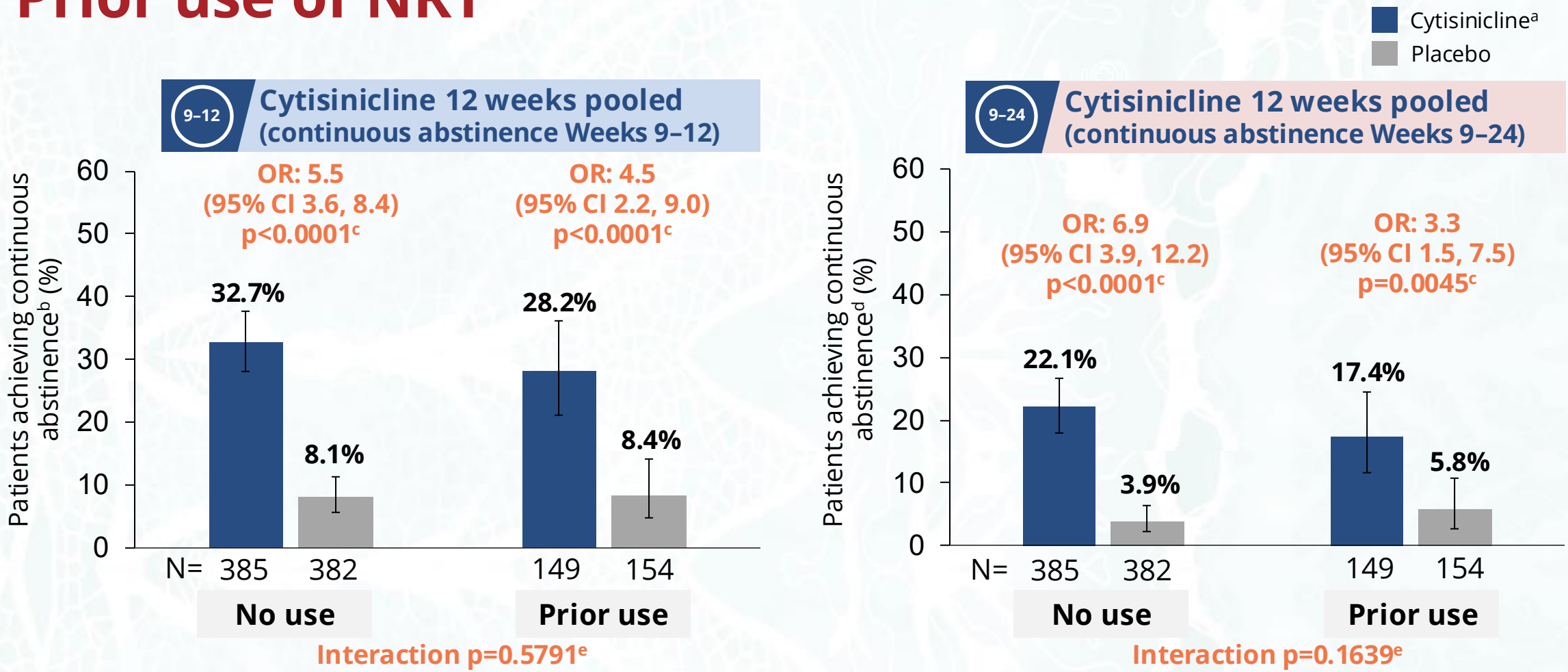
[a]Participants received cytisinicline 3 mg TID; [b]Participants who achieved 4 weeks of continuous CO-verified smoking abstinence during the last 4 weeks of the 12-week treatment (Weeks 9–12); [c]Two-sided p-value for the treatment effect derived from a logistic regression model adjusted for age, sex, smoking duration, and number of prior quit attempts; [d]Participants who achieved continuous CO-verified smoking abstinence (Weeks 9–24); [e]Two-sided p-value for the interaction between the treatment effect and subgroup factor derived from a logistic regression model with the additional interaction term.
CI, confidence interval; CO, carbon monoxide; OR, odds ratio; TID, three times daily.

Prior use of bupropion



[a]Participants received cytisinicline 3 mg TID; [b]Participants who achieved 4 weeks of continuous CO-verified smoking abstinence during the last 4 weeks of the 12-week treatment (Weeks 9–12); [c]Two-sided p-value for the treatment effect derived from a logistic regression model adjusted for age, sex, smoking duration, and number of prior quit attempts; [d]Participants who achieved continuous CO-verified smoking abstinence (Weeks 9–24); [e]Two-sided p-value for the interaction between the treatment effect and subgroup factor derived from a logistic regression model with the additional interaction term.
CI, confidence interval; CO, carbon monoxide; OR, odds ratio; TID, three times daily.

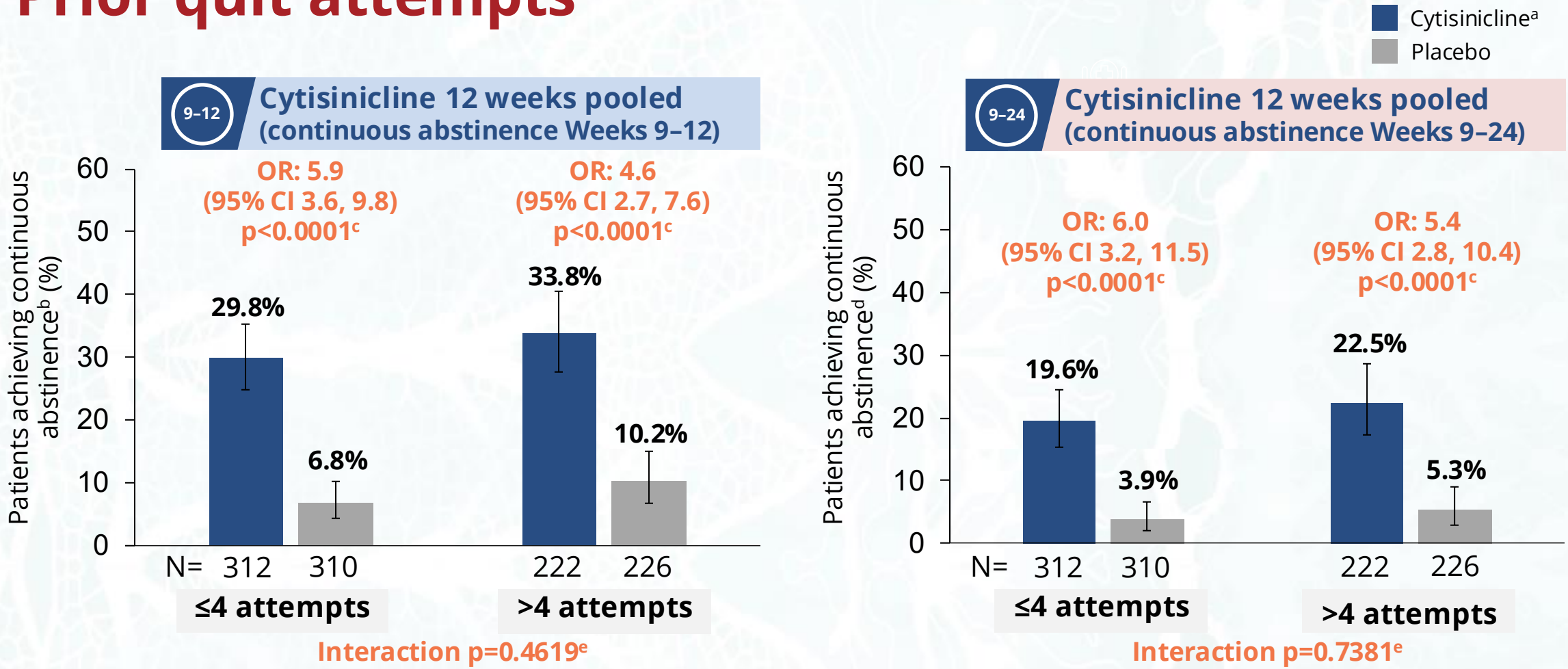
Prior use of NRT



[a]Participants received cytisinicline 3 mg TID; [b]Participants who achieved 4 weeks of continuous CO-verified smoking abstinence during the last 4 weeks of the 12-week treatment (Weeks 9–12); [c]Two-sided p-value for the treatment effect derived from a logistic regression model adjusted for age, sex, smoking duration, and number of prior quit attempts; [d]Participants who achieved continuous CO-verified smoking abstinence (Weeks 9–24); [e]Two-sided p-value for the interaction between the treatment effect and subgroup factor derived from a logistic regression model with the additional interaction term.

CI, confidence interval; CO, carbon monoxide; NRT, nicotine replacement therapy; OR, odds ratio; TID, three times daily.

Prior quit attempts



[a]Participants received cytisinicline 3 mg TID; [b]Participants who achieved 4 weeks of continuous CO-verified smoking abstinence during the last 4 weeks of the 12-week treatment (Weeks 9–12); [c]Two-sided p-value for the treatment effect derived from a logistic regression model adjusted for age, sex, and smoking duration; [d]Participants who achieved continuous CO-verified smoking abstinence (Weeks 9–24); [e]Two-sided p-value for the interaction between the treatment effect and subgroup factor derived from a logistic regression model with the additional interaction term.

CI, confidence interval; CO, carbon monoxide; OR, odds ratio; TID, three times daily.

Safety

All TEAEs,[b] n (%)	Varenicline[a]			
	No use		Prior use	
	Cytisinicline 12 weeks N=301[c]	Placebo N=309	Cytisinicline 12 weeks N=229[c]	Placebo N=223
Insomnia	25 (8.3)	16 (5.2)	32 (14.0)	17 (7.6)
Abnormal dreams	14 (4.7)	10 (3.2)	27 (11.8)	13 (5.8)
Headache	24 (8.0)	22 (7.1)	19 (8.3)	16 (7.2)
Nausea	13 (4.3)	23 (7.4)	20 (8.7)	16 (7.2)

12 weeks of cytisinicline were generally well tolerated across treatment subgroups, regardless of prior treatment or previous quit attempt

[a]Safety population from phase 3 pool from ORCA-2 and ORCA phase 3 studies; [b]All TEAEs occurring in ≥7% of patients in any group. TEAEs of COVID-19 were also reported;
[c]All patients receiving cytisinicline 3 mg TID for 12 weeks.
COVID-19, coronavirus disease of 2019; TEAE, treatment-emergent adverse event; TID, three times daily.

Limitation

This was a post hoc analysis of data from the ORCA-2 and ORCA-3 trials, and is therefore subject to the inherent limitations of retrospective stratification

Summary and conclusion

- Cytisinicline treatment for **12 weeks** vs placebo resulted in a greater proportion of participants achieving continuous smoking abstinence for the last 4 weeks of treatment and extending to Week 24 in all subgroups evaluated:
  - With or without prior use of varenicline, bupropion, or NRT for smoking cessation
  - With ≤4 or >4 or previous quit attempts
- Similarly (data not presented), participants treated with **6 weeks** of cytisinicline vs placebo also achieved higher rates of continuous abstinence at the end of treatment and up to Week 24, regardless of prior use of smoking cessation medications or number of quit attempts
- Both 6 and 12 weeks of cytisinicline were generally well tolerated across treatment groups

Cytisinicline was effective and well tolerated regardless of prior use of smoking cessation medications or number of previous quit attempts

NRT, nicotine replacement therapy.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APPENDICES

Baseline characteristics

Characteristic	Varenicline		Bupropion		NRT	
	No use (N=931)	Prior use (N=671)	No use (N=1279)	Prior use (N=323)	No use (N=1147)	Prior use (N=455)
Prior varenicline use, n (%)	-	-	**474 (37.1)**	**197 (61.0)**	492 (42.9)	179 (39.3)
Prior bupropion use, n (%)	**126 (13.5)**	**197 (29.4)**	-	-	**216 (18.8)**	**107 (23.5)**
Prior use of NRT, n (%)	276 (29.6)	179 (26.7)	**348 (27.2)**	**107 (33.1)**	-	-
Prior quit attempts, n (%)						
≤4 attempts	**604 (64.9)**	**328 (48.9)**	**789 (61.7)**	**143 (44.3)**	659 (57.5)	273 (60.0)
>4 attempts	**327 (35.1)**	**343 (51.1)**	**490 (38.3)**	**180 (55.7)**	488 (42.5)	182 (40.0)

Two-sided p-value and an F-test for numeric variables; bold for $p<0.05$.
NRT, nicotine replacement therapy.

Baseline characteristics

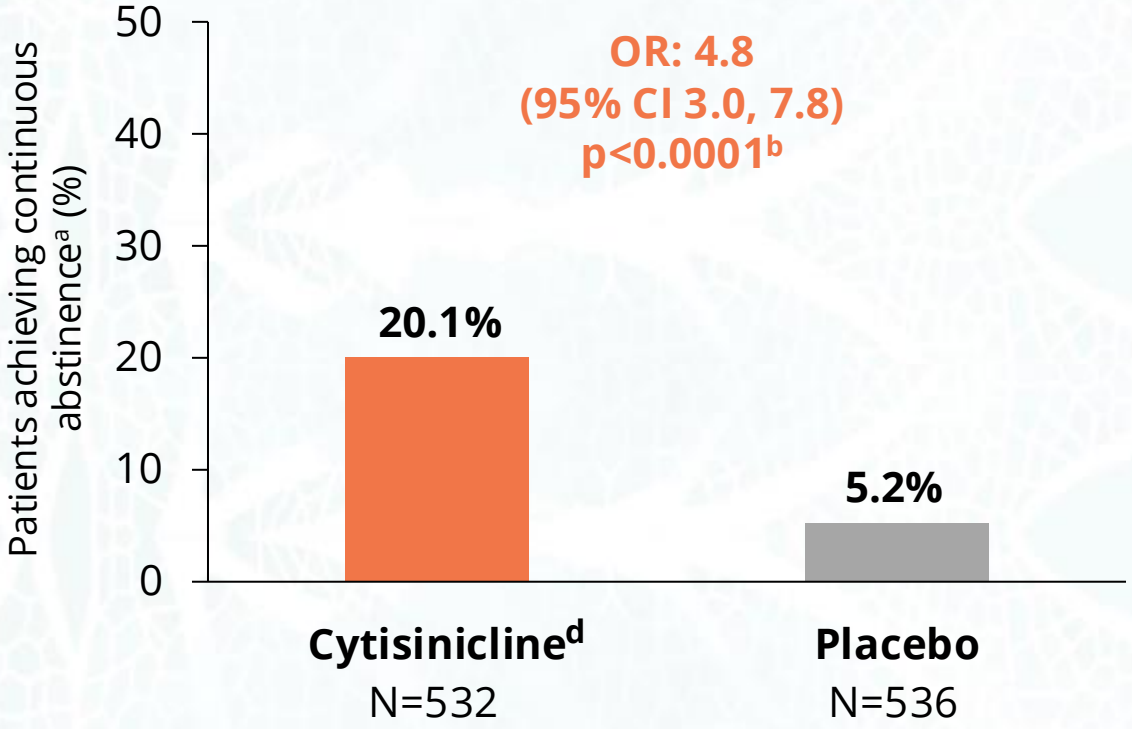
Characteristic	Number of prior quit attempts	
	≤4 attempts (N=932)	>4 attempts (N=670)
Prior varenicline use, n (%)	**328 (35.2)**	**343 (51.2)**
Prior bupropion use, n (%)	**143 (15.3)**	**180 (26.9)**
Prior use of NRT, n (%)	273 (29.3)	182 (27.2)

Two-sided p-value and an F-test for numeric variables; bold for $p<0.05$.
NRT, nicotine replacement therapy.

Smoking abstinence for 6-week treatment

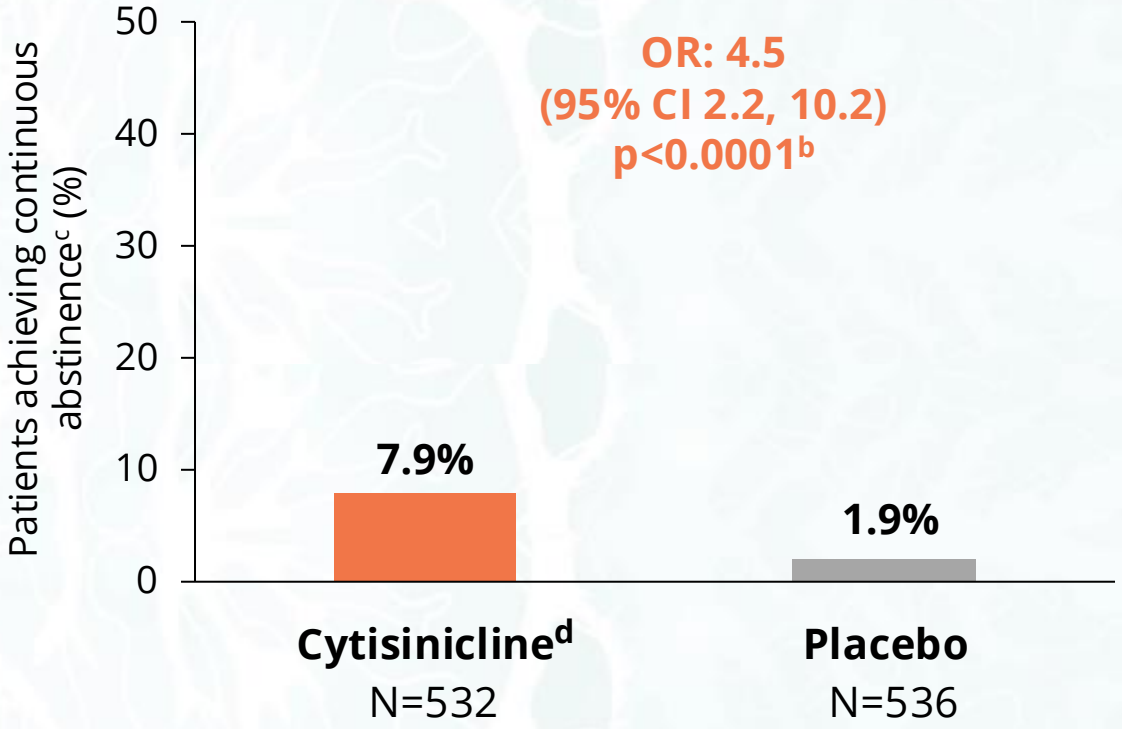
Primary endpoint

3–6 Cytisinicline 6 weeks only pooled (continuous abstinence Weeks 3–6)



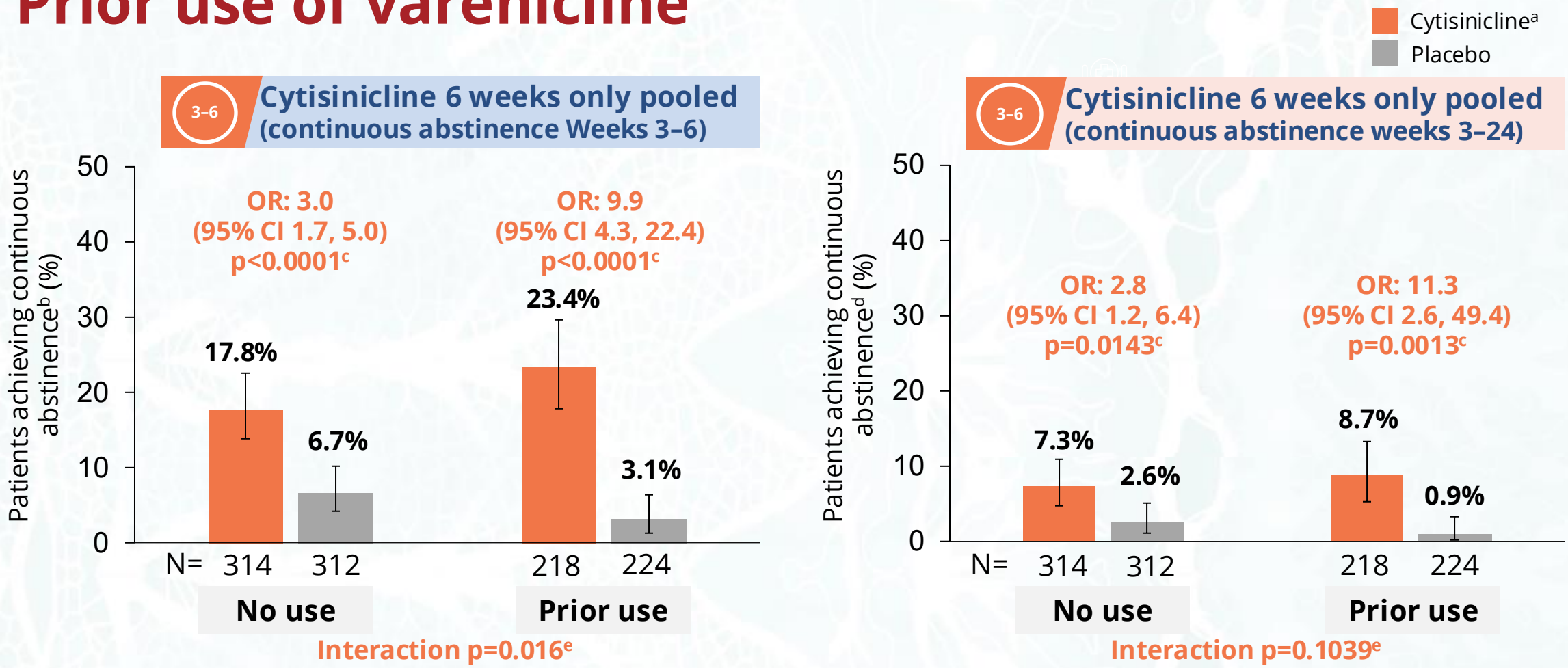
Secondary endpoint

3–24 Cytisinicline 6 weeks only pooled (continuous abstinence Weeks 3–24)



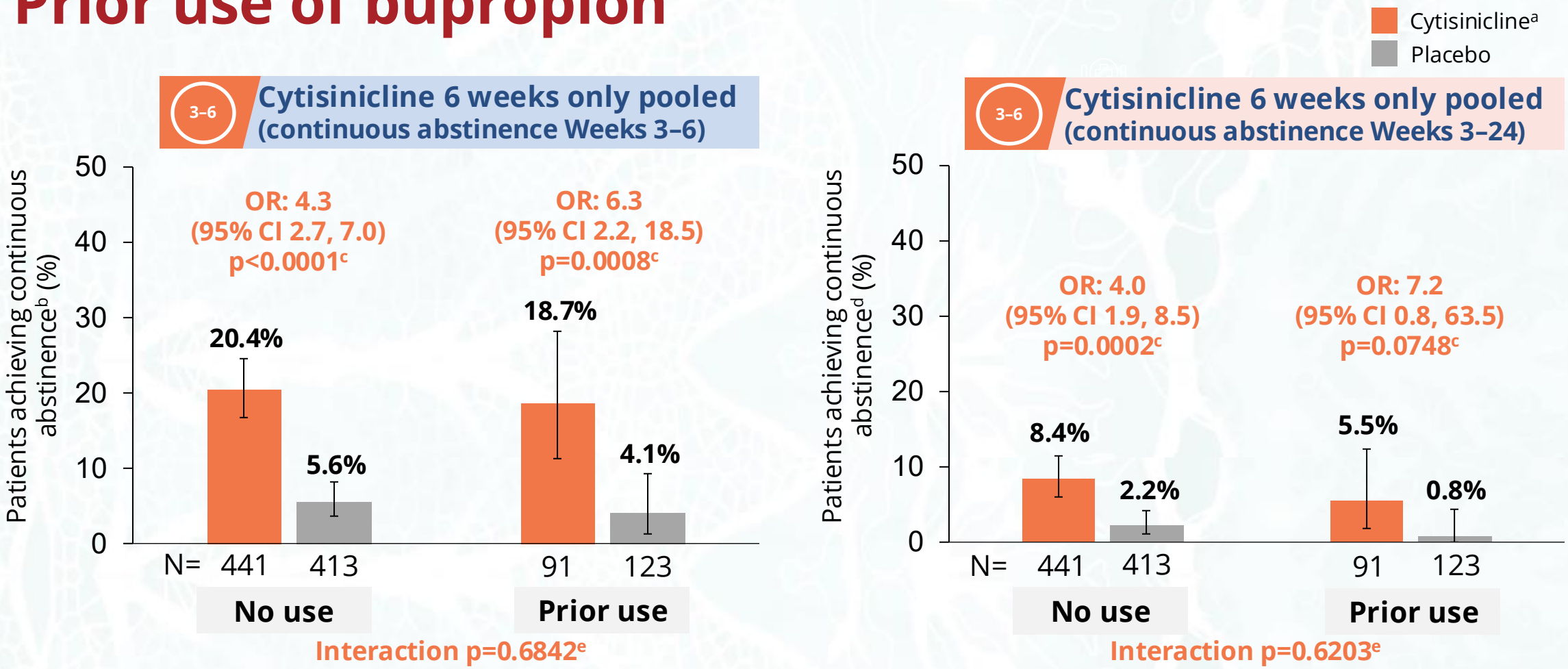
[a]Participants who achieved 4 weeks of continuous CO-verified smoking abstinence from Week 3 to Week 6; [b]P-value for differences in proportion, via Cochran-Mantel-Haenszel test; [c]Participants who achieved continuous CO-verified smoking abstinence from Week 3 to Week 24; [d]Participants received cytisinicline 3 mg TID.
CI, confidence interval; CO, carbon monoxide; OR, odds ratio; TID, three times daily.

Prior use of varenicline



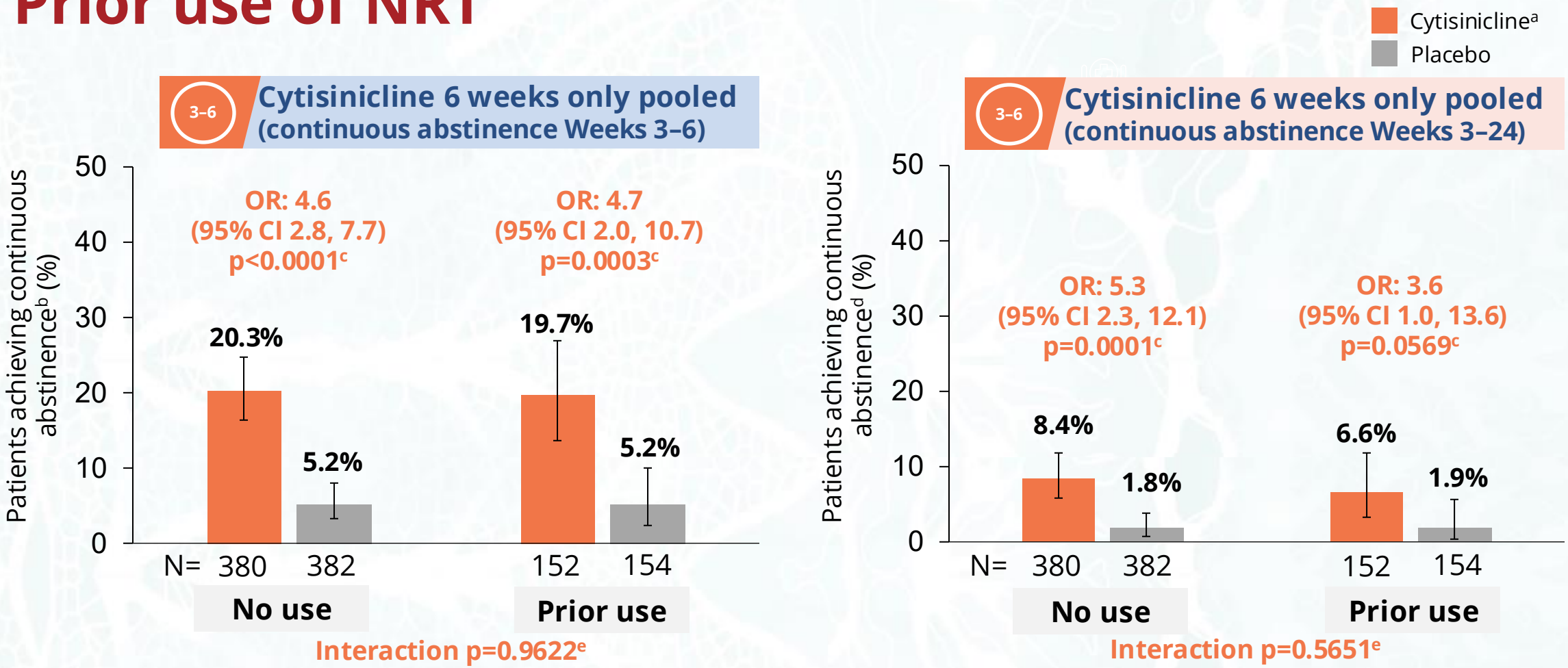
[a]Participants received cytisinicline 3 mg TID; [b]Participants who achieved 4 weeks of continuous CO-verified smoking abstinence during the last 4 weeks of the 6-week treatment (Weeks 3–6); [c]Two-sided p-value for the treatment effect derived from a logistic regression model adjusted for age, sex, smoking duration, and number of prior quit attempts; [d]Participants who achieved continuous CO-verified smoking abstinence (Weeks 3–24); [e]Two-sided p-value for the interaction between the treatment effect and subgroup factor derived from a logistic regression model with the additional interaction term.
CI, confidence interval; CO, carbon monoxide; OR, odds ratio; TID, three times daily.

Prior use of bupropion



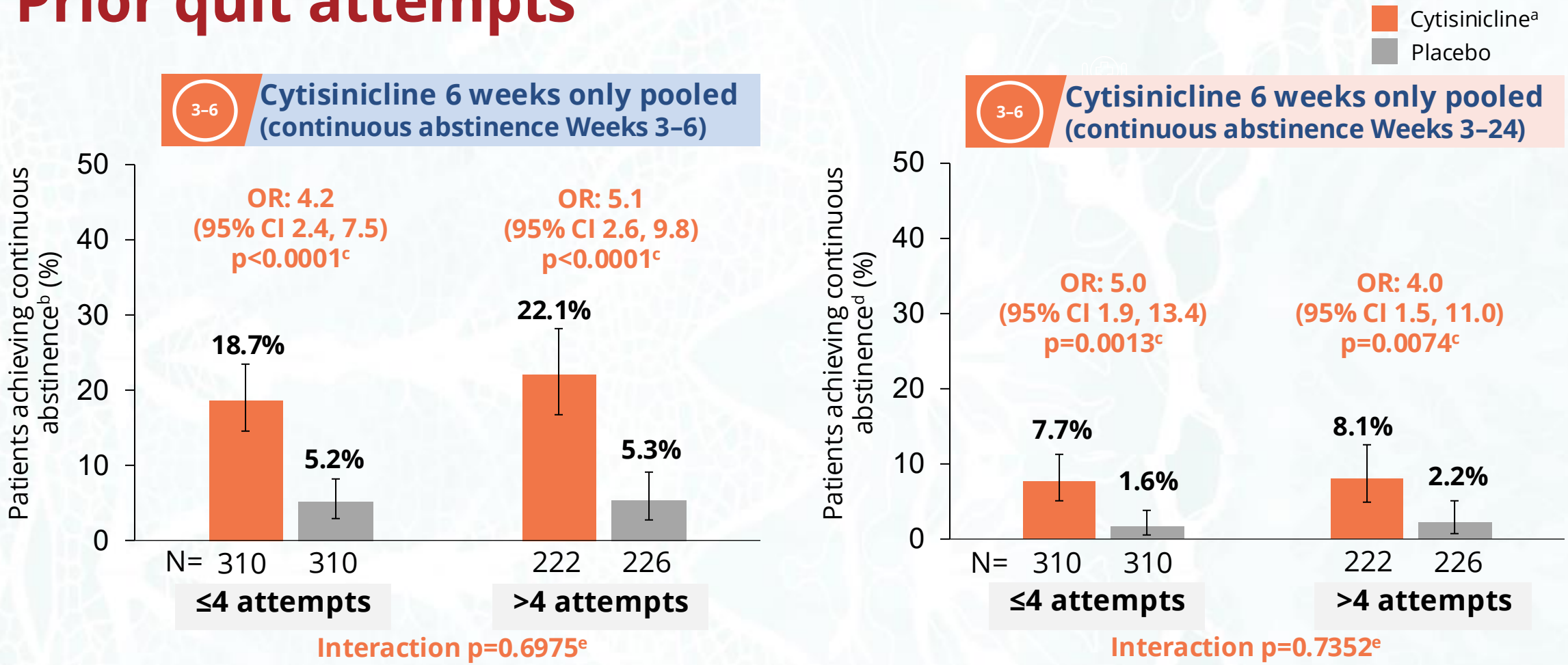
[a]Participants received cytisinicline 3 mg TID; [b]Participants who achieved 4 weeks of continuous CO-verified smoking abstinence during the last 4 weeks of the 6-week treatment (Weeks 3–6); [c]Two-sided p-value for the treatment effect derived from a logistic regression model adjusted for age, sex, smoking duration, and number of prior quit attempts; [d]Participants who achieved continuous CO-verified smoking abstinence (Weeks 3–24); [e]Two-sided p-value for the interaction between the treatment effect and subgroup factor derived from a logistic regression model with the additional interaction term.
CI, confidence interval; CO, carbon monoxide; OR, odds ratio; TID, three times daily.

Prior use of NRT



[a]Participants received cytisinicline 3 mg TID; [b]Participants who achieved 4 weeks of continuous CO-verified smoking abstinence during the last 4 weeks of the 6-week treatment (Weeks 3–6); [c]Two-sided p-value for the treatment effect derived from a logistic regression model adjusted for age, sex, smoking duration, and number of prior quit attempts; [d]Participants who achieved continuous CO-verified smoking abstinence (Weeks 3–24); [e]Two-sided p-value for the interaction between the treatment effect and subgroup factor derived from a logistic regression model with the additional interaction term.
CI, confidence interval; CO, carbon monoxide; NRT, nicotine replacement therapy; OR, odds ratio; TID, three times daily.

Prior quit attempts



[a]Participants received cytisinicline 3 mg TID; [b]Participants who achieved 4 weeks of continuous CO-verified smoking abstinence during the last 4 weeks of the 6-week treatment (Weeks 3–6); [c]Two-sided p-value for the treatment effect derived from a logistic regression model adjusted for age, sex, and smoking duration; [d]Participants who achieved continuous CO-verified smoking abstinence (Weeks 3–24); [e]Two-sided p-value for the interaction between the treatment effect and subgroup factor derived from a logistic regression model with the additional interaction term.
CI, confidence interval; CO, carbon monoxide; OR, odds ratio; TID, three times daily.

Safety: 12 weeks of cytisinicline

Cytisinicline 12 weeks[a] Placebo

All TEAEs[b], n (%)	Varenicline				Bupropion				NRT				Number of prior quit attempts			
	No use		Prior use		No use		Prior use		No use		Prior use		≤4 prior quit attempts		>4 prior quit attempts	
	N=301	N=309	N=229	N=223	N=421	N=409	N=109	N=123	N=383	N=379	N=147	N=153	N=309	N=307	N=221	N=225
Abnormal dreams	14 (4.7)	10 (3.2)	27 (11.8)	13 (5.8)	34 (8.1)	15 (3.7)	7 (6.4)	8 (6.5)	35 (9.1)	18 (4.7)	6 (4.1)	5 (3.3)	24 (7.8)	13 (4.2)	17 (7.7)	10 (4.4)
Fatigue	-	-	-	-	13 (3.1)	4 (1.0)	8 (7.3)	3 (2.4)	-	-	-	-	-	-	-	-
Headache	24 (8.0)	22 (7.1)	19 (8.3)	16 (7.2)	37 (8.8)	29 (7.1)	6 (5.5)	9 (7.3)	32 (8.4)	28 (7.4)	11 (7.5)	10 (6.5)	19 (6.1)	22 (7.2)	24 (10.9)	16 (7.1)
Insomnia	25 (8.3)	16 (5.2)	32 (14.0)	17 (7.6)	49 (11.6)	25 (6.1)	8 (7.3)	8 (6.5)	47 (12.3)	26 (6.9)	10 (6.8)	7 (4.6)	28 (9.1)	13 (4.2)	29 (13.1)	20 (8.9)
Nausea	13 (4.3)	23 (7.4)	20 (8.7)	16 (7.2)	28 (6.7)	32 (7.8)	5 (4.6)	7 (5.7)	24 (6.3)	25 (6.6)	9 (6.1)	14 (9.2)	22 (7.1)	21 (6.8)	11 (5.0)	18 (8.0)

Safety population from phase 3 pool from ORCA-2 and ORCA phase 3 studies; [a]All patients receiving cytisinicline 3 mg TID for 12 weeks; [b]All TEAEs occurring in ≥7% of patients in any group. TEAEs of COVID-19 were also reported.
COVID-19, coronavirus disease of 2019; NRT, nicotine replacement therapy; TEAE, treatment-emergent adverse event; TID, three times daily.

Safety: 6 weeks of cytisinicline

Cytisinicline 6 weeks[a] | Placebo

All TEAEs[b], n (%)	Varenicline				Bupropion				NRT				Number of prior quit attempts			
	No use		Prior use		No use		Prior use		No use		Prior use		≤4 prior quit attempts		>4 prior quit attempts	
	N=314	N=309	N=218	N=223	N=441	N=409	N=91	N=123	N=380	N=379	N=152	N=153	N=310	N=307	N=222	N=225
Abnormal dreams	21 (6.7)	10 (3.2)	25 (11.5)	13 (5.8)	39 (8.8)	15 (3.7)	7 (7.7)	8 (6.5)	33 (8.7)	18 (4.7)	13 (8.6)	5 (3.3)	30 (9.7)	13 (4.2)	16 (7.2)	10 (4.4)
Headache	20 (6.4)	22 (7.1)	18 (8.3)	16 (7.2)	31 (7.0)	29 (7.1)	7 (7.7)	9 (7.3)	23 (6.1)	28 (7.4)	15 (9.9)	10 (6.5)	17 (5.5)	22 (7.2)	21 (9.5)	16 (7.1)
Insomnia	32 (10.2)	16 (5.2)	20 (9.2)	17 (7.6)	42 (9.5)	25 (6.1)	10 (11.0)	8 (6.5)	36 (9.5)	26 (6.9)	16 (10.5)	7 (4.6)	27 (8.7)	13 (4.2)	25 (11.3)	20 (8.9)
Nausea	23 (7.3)	23 (7.4)	18 (8.3)	16 (7.2)	31 (7.0)	32 (7.8)	10 (11.0)	7 (5.7)	26 (6.8)	25 (6.6)	15 (9.9)	14 (9.2)	22 (7.1)	21 (6.8)	19 (8.6)	18 (8.0)

Safety population from phase 3 pool from ORCA-2 and ORCA phase 3 studies; [a]All patients receiving cytisinicline 3 mg TID for 6 weeks then placebo for 6 weeks;
[b]All TEAEs occurring in ≥7% patients in any group. TEAEs of COVID-19 were also reported.
COVID-19, coronavirus disease of 2019; NRT, nicotine replacement therapy; TEAE, treatment-emergent adverse event; TID, three times daily.