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Achieve Life Sciences
NASDAQ: ACHV

July 2026

Forward Looking Statements

This presentation contains forward-looking statements, including, but not limited to, statements regarding the timing and nature of cytisinicline clinical development and regulatory review and approval; data results and commercialization strategy and activities; the potential market size for cytisinicline; the potential benefits, efficacy, safety and tolerability of cytisinicline; the ability to discover and develop new uses for cytisinicline, including but not limited to as an e-cigarette cessation product; the development and effectiveness of new treatments; the successful commercialization of cytisinicline; and expectations regarding cash uses and forecasts. All statements other than statements of historical fact are statements that could be deemed forward-looking statements. Achieve Life Sciences, Inc. ("we," "us," "our," or "the Company") may not actually achieve its plans or product development goals in a timely manner, if at all, or otherwise carry out the intentions or meet the expectations or projections disclosed in these forward-looking statements. These statements are based on management's current expectations and beliefs and are subject to a number of risks, uncertainties and assumptions that could cause actual results to differ materially from those described in the forward-looking statements, including, among others, the risk that cytisinicline may not demonstrate the hypothesized or expected benefits; the risk that we may not be able to obtain additional financing to fund the development and commercialization of cytisinicline; the risk that cytisinicline will not receive regulatory approval in a timely manner or at all, or be successfully commercialized; the risk that new developments in the smoking and vaping cessation landscapes require changes in business strategy or clinical development plans; the risk that our intellectual property may not be adequately protected; general business and economic conditions; risks related to the impact on our business of macroeconomic and geopolitical conditions, including fluctuating inflation, interest and tariff rates, volatility in the debt and equity markets, actual or perceived instability in the global banking system, global health crises and pandemics and geopolitical conflict; and the other factors described in the risk factors set forth in the Company's filings with the Securities and Exchange Commission from time to time, including its Annual Reports on Form 10-K and Quarterly Reports on Form 10-Q. The Company undertakes no obligation to update the forward-looking statements contained herein or to reflect events or circumstances occurring after the date hereof, other than as may be required by applicable law.

These slides also contain estimates and other statistical data made by independent parties and by us relating to market size and growth and other data about our industry. This data involves a number of assumptions and limitations, and you are cautioned not to give undue weight to such estimates. In addition, projections, assumptions, and estimates of our future performance and the future performance of the markets in which we operate are necessarily subject to a high degree of uncertainty and risk.

Certain data in this presentation are based on cross-study comparisons and are not based on any head-to-head clinical trials. Cross-study comparisons are inherently limited and may suggest misleading similarities and differences. The values shown in the cross-study comparisons are directional and may not be directly comparable.

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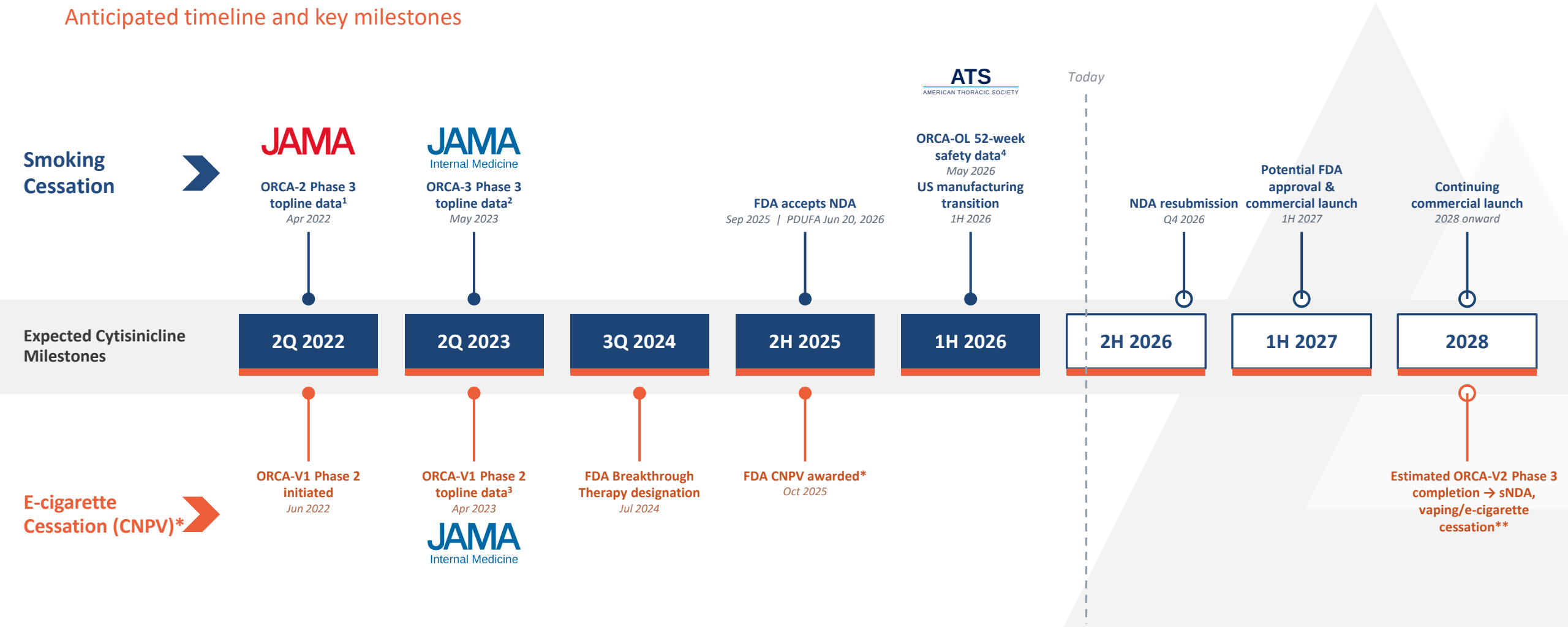
Cytisinicline

After two decades without meaningful innovation in U.S. smoking cessation, cytisinicline demonstrated potential best-in-class efficacy and an excellent safety profile — even in the hardest-to-treat patients.

Driving toward regulatory approval and launch

Anticipated timeline and key milestones



[1] ORCA-2 (smoking, Phase 3): topline Apr 2022; published in JAMA, Jul 11, 2023. Rigotti NA, et al. JAMA. 2023;330(2):152-160. doi:10.1001/jama.2023.10042
[2] ORCA-3 (smoking, Phase 3): topline May 2023; published in JAMA Internal Medicine, Apr 21, 2025. Rigotti NA, et al. JAMA Intern Med. 2025. doi:10.1001/jamainternmed.2025.0628
[3] ORCA-V1 (vaping, Phase 2): topline Apr 2023; published in JAMA Internal Medicine, May 6, 2024. Rigotti NA, et al. JAMA Intern Med. 2024. doi:10.1001/jamainternmed.2024.1313
[4] ORCA-OL 52-week safety data presented at the American Thoracic Society (ATS) 2026 International Conference, May 15-20, 2026, Orlando, FL. Poster #325; Rigotti NA, et al.

Timeline reflects current management expectations, which are subject to change and are not guarantees of future results. * Commissioner's National Priority Voucher (CNPV). ** ORCA-V2 e-cigarette cessation program timeline is best estimate.

Recent developments: well-capitalized with a proven launch team

New financing, the Ohtuvayre commercial team, and three new independent directors

WELL-CAPITALIZED

Apr 2026

Up to

$354M

in total financing

$180M upfront plus up to **$174M** in milestone-driven warrants exercisable within 20 days of FDA approval.

Lucian Iancovici, MD
Incoming Chairman of the Board, Partner TPG Growth

Aaron Royston, MD
Board Director, Managing Partner VenBio Partners

Led by Frazier Life Sciences, TPG Life Sciences Innovations, venBio Partners, Paradigm BioCapital Advisors, and Marshall Wace, with Janus Henderson, Wellington, Venrock, and Vivo among participants.

COMMERCIAL EXPERIENCE

May 2026

Reunites the team behind the Ohtuvayre® launch

Christopher Martin
Board of Directors · former CCO, Verona Pharma

Mark Zappia
SVP, Commercial

Jim Willis
VP, Sales & Sales Enablement

Verona Pharma acquired by Merck for $10.8B (Oct 2025); Ohtuvayre was among the most successful specialty launches in recent history.

STRENGTHENED BOARD

Jun 2026

Two new independent directors

Jeff Farrow
CFO & CSO, Tarsus Pharmaceuticals

Reid Waldman, MD
CEO, Veradermics

Adds public-company finance, corporate strategy, and biotech CEO leadership ahead of launch.

Source: Company press releases, 2026.

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The Market

A large, underserved U.S. nicotine-dependence market

A large nicotine-dependent population

~48M[1]
U.S. tobacco / nicotine users

~38M[1]
Smokers and/or vapers

25M[1]
Adult cigarette smokers

~18M[1]
E-cigarette (vape) users

Most try to quit, and most fail

~15M[4]
Attempt to quit each year

~14M[4]
Fail to quit each year

10.5M[3]
Cessation prescriptions filled annually

Decades without a new therapy

0[2]
New smoking-cessation therapies approved in ~20 years (last FDA approval: varenicline, 2006)

0[5]
FDA-approved therapies for vaping cessation (none ever approved)

[1] Agaku I. Tobacco Product Use among U.S. Adults, 2023-2024. NEJM Evidence 2026. doi:10.1056/EVIDpha2500339 (47.7M any tobacco product; 25.2M cigarette; 17.8M e-cigarette users).
[2] U.S. Public Health Service, Office of the Surgeon General. Smoking Cessation: A Report of the Surgeon General. HHS; 2020. No new FDA-approved smoking-cessation medication since varenicline (2006).
[3] Symphony Health smoking-cessation prescription claims data, Jan-Dec 2025.
[4] CDC. Smoking Cessation: Fast Facts, 2022 (~53% of adults who smoke make a quit attempt annually; fewer than 1 in 10 succeed).
[5] No pharmacotherapy is FDA-approved as an aid to e-cigarette (vaping) cessation (U.S. FDA).

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Nicotine dependence is a costly and growing medical problem

Smoking's toll on the U.S.

$600B[1]

Annual U.S. economic cost of smoking (~$240B of it in direct health care)

480,000+[2]

U.S. deaths each year, the #1 cause of preventable death

Vaping: a rising public health crisis

~90%[3]

growth in U.S. adult vaping since 2020

~1 in 7[4,5]

U.S. adults aged 18-34 vape, with 21-24 being the highest rate of any age group (15.5%)

And most users want to quit

~68%[6]

of U.S. adults who smoke want to quit

~60%[7]

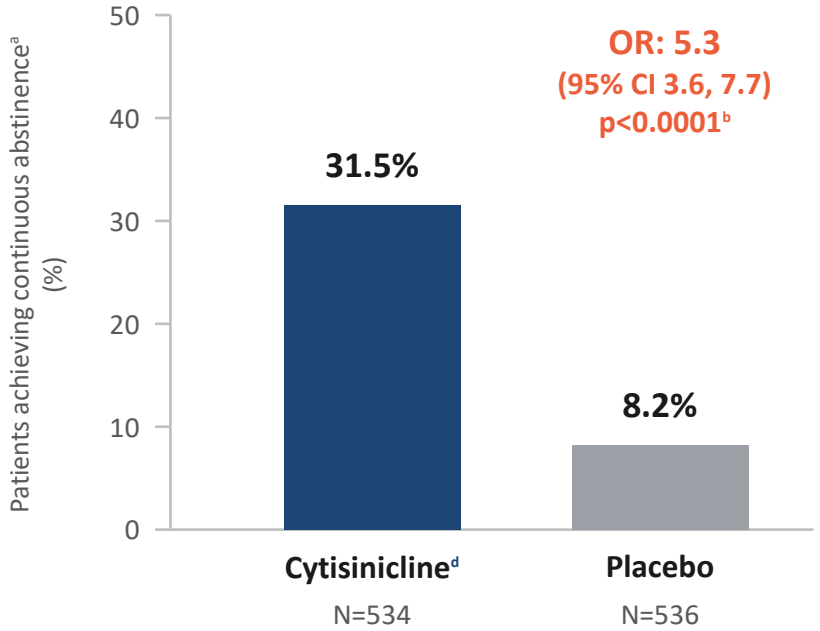
of U.S. adults who vape plan to quit

[1] CDC. Economic Trends in Tobacco. Cigarette smoking cost the U.S. >$600B in 2018, including >$240B in health care spending and ~$360B in lost productivity.
[2] CDC. Commercial tobacco use is the leading cause of preventable disease and death in the U.S.; cigarette smoking causes >480,000 deaths annually.
[3] Adult e-cigarette use rose from 3.7% (2020) to 7.0% (2024). CDC; Agaku I, NEJM Evidence 2026, doi:10.1056/EVIDpha2500339.
[4] National Center for Health Statistics. Percentage of current electronic cigarette use for adults aged 18 and over, United States, 2019—2024. National Health Interview Survey. Generated interactively: Jun 01 2026 from https://wwwn.cdc.gov/NHISDataQueryTool/SHS_adult/index.ht.
[5] CDC. https://www.cdc.gov/nchs/data/databriefs/db524.pdf
[6] CDC. Smoking Cessation: Fast Facts, 2022: 67.7% of adults who smoke reported wanting to quit.
[7] CDC. E-Cigarette Use Among Adults: 60.1% of adults who currently vape reported plans to quit (2016-2018 study).

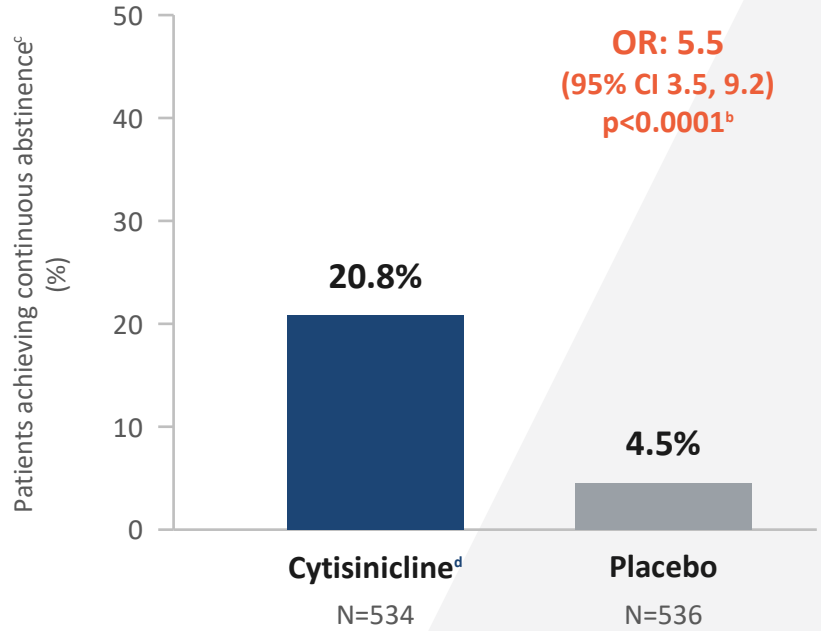
Across multiple Phase 3 trials, 12 weeks of cytisinicline demonstrated best-in-class odds of quitting smoking[1,2]

PUBLISHED IN JAMA JAMA Internal Medicine

Primary endpoint | **Cytisinicline 12 weeks pooled (continuous abstinence, weeks 9-12)**



Secondary endpoint | **Cytisinicline 12 weeks pooled (continuous abstinence, weeks 9-24)**



78% drug adherence for the 12-week course in ORCA Phase 3 studies

[1] Rigotti NA, et al. Cytisinicline for Smoking Cessation: The ORCA Phase 3 Replication Randomized Clinical Trial (ORCA-3). JAMA Intern Med. 2025;185(6):648-655. doi:10.1001/jamainternmed.2025.0628
[2] Rigotti NA, et al. Cytisinicline for Smoking Cessation: A Randomized Clinical Trial (ORCA-2). JAMA. 2023;330(2):152-160. doi:10.1001/jama.2023.10042

[a] Continuous CO-verified abstinence, Week 9-12; b P-value via Cochran-Mantel-Haenszel test; c Continuous CO-verified abstinence, Week 9-24; d Cytisinicline 3 mg TID. CI, confidence interval; CO, carbon monoxide; OR, odds ratio; TID, three times daily.

From: **Cytisinicline for Smoking Cessation: A Randomized Clinical Trial**
JAMA. 2023;330(2):152-160. doi:10.1001/jama.2023.10042

JAMA Network™

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. (%)[a]			
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[b]	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. (%)[c]	30 (11.1)	25 (9.3)	23 (8.5)
Comorbidities			
Hospital Anxiety and Depression Scale total score, mean (SD)[d]	5.5 (4.5)	5.4 (3.7)	5.5 (4.2)

[a] Race and ethnicity were assessed by a participant's response to a fixed-category question.

[b] Fagerstrom Test for Nicotine Dependence[17] 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.

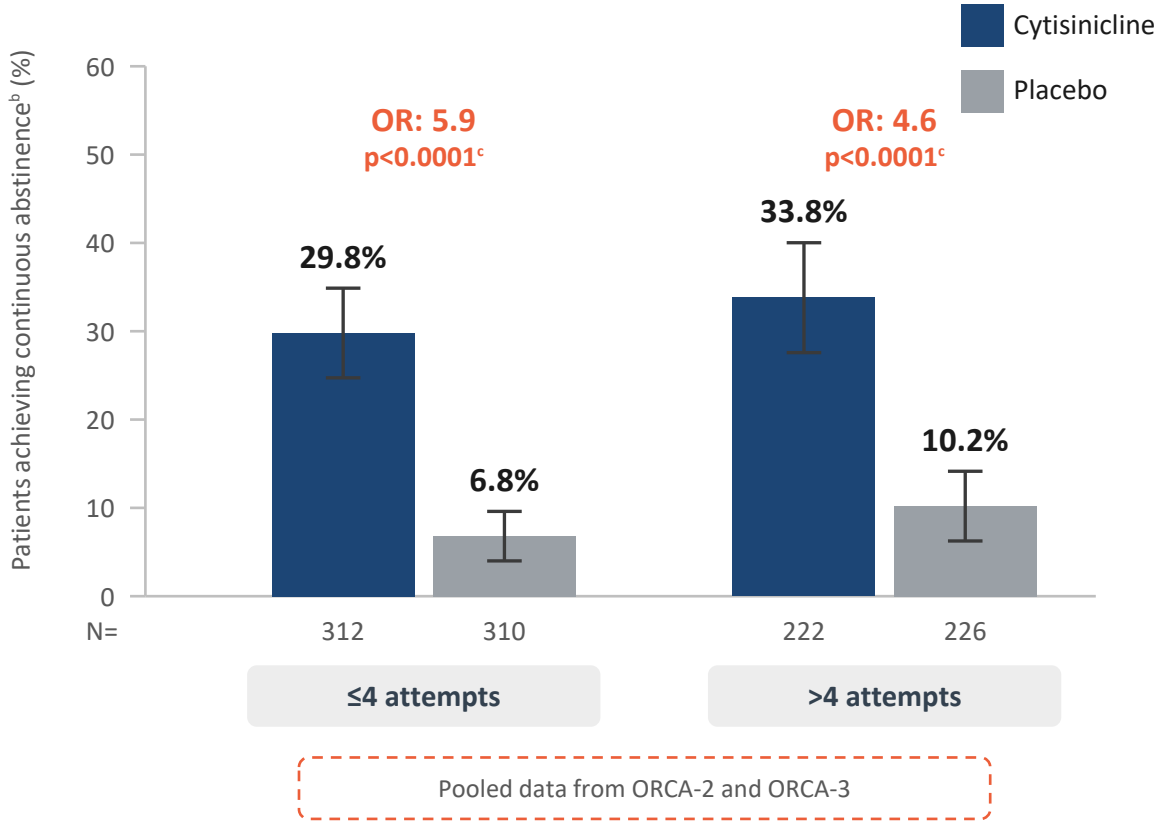
[c] Includes counseling support received in person, by phone, or via web.

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

Cytisinicline demonstrated efficacy regardless of number of prior quit attempts[1]

SOCIETY FOR RESEARCH ON NICOTINE & TOBACCO
Presented Baltimore, 2026

Primary endpoint | **Continuous abstinence[a], weeks 9-12**



Pooled data from ORCA-2 and ORCA-3

Nearly

~4 to 6-fold

higher odds of cessation

regardless of number of prior quit attempts

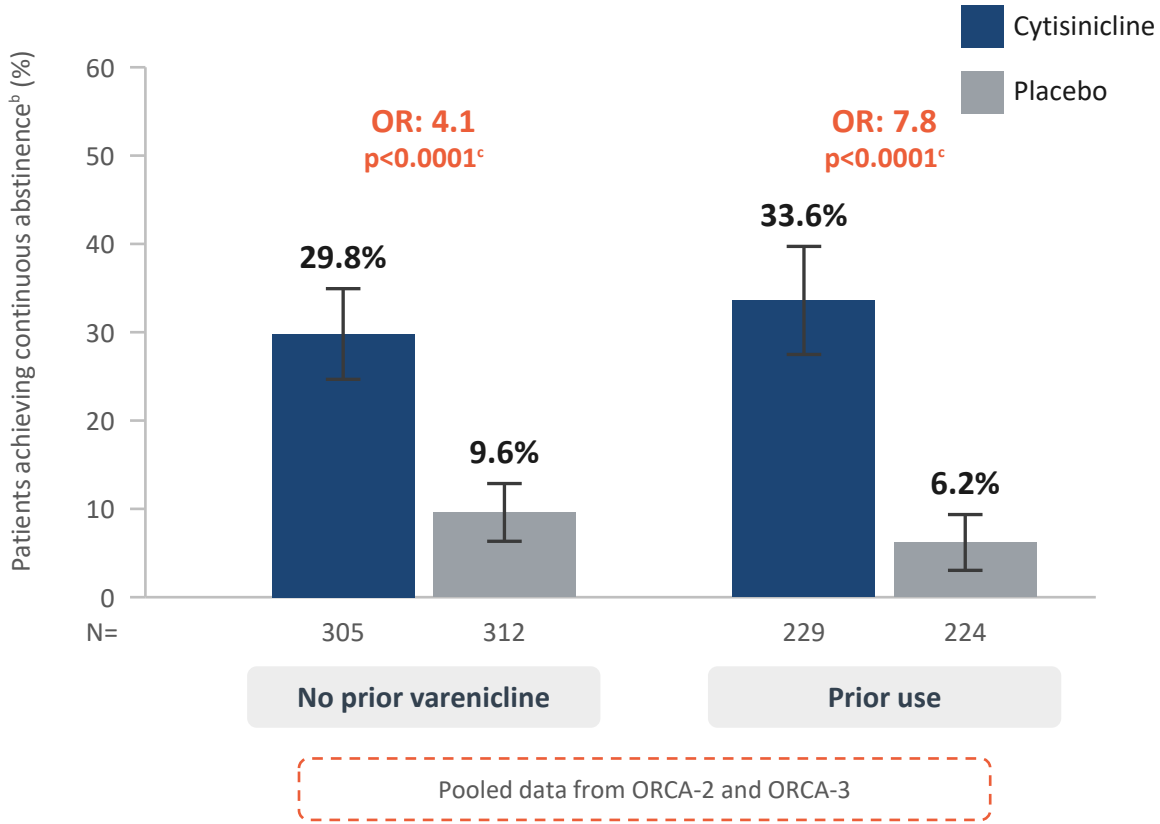
[1] Data presented at the Society for Research on Nicotine & Tobacco (SRNT) Annual Meeting, March 2026. https://achievelifesciences.com/products/resources/

[a] Continuous CO-verified smoking abstinence, Week 9-12; b P-value for difference in proportion, via Cochran-Mantel-Haenszel test; c vs placebo. Error bars represent 95% CI. CO, carbon monoxide; OR, odds ratio.

Cytisinicline demonstrated efficacy regardless of prior varenicline use[1]

SOCIETY FOR RESEARCH ON NICOTINE & TOBACCO
Presented Baltimore, 2026

Primary endpoint | **Continuous abstinence[a], weeks 9-12**



Approximately

8-fold

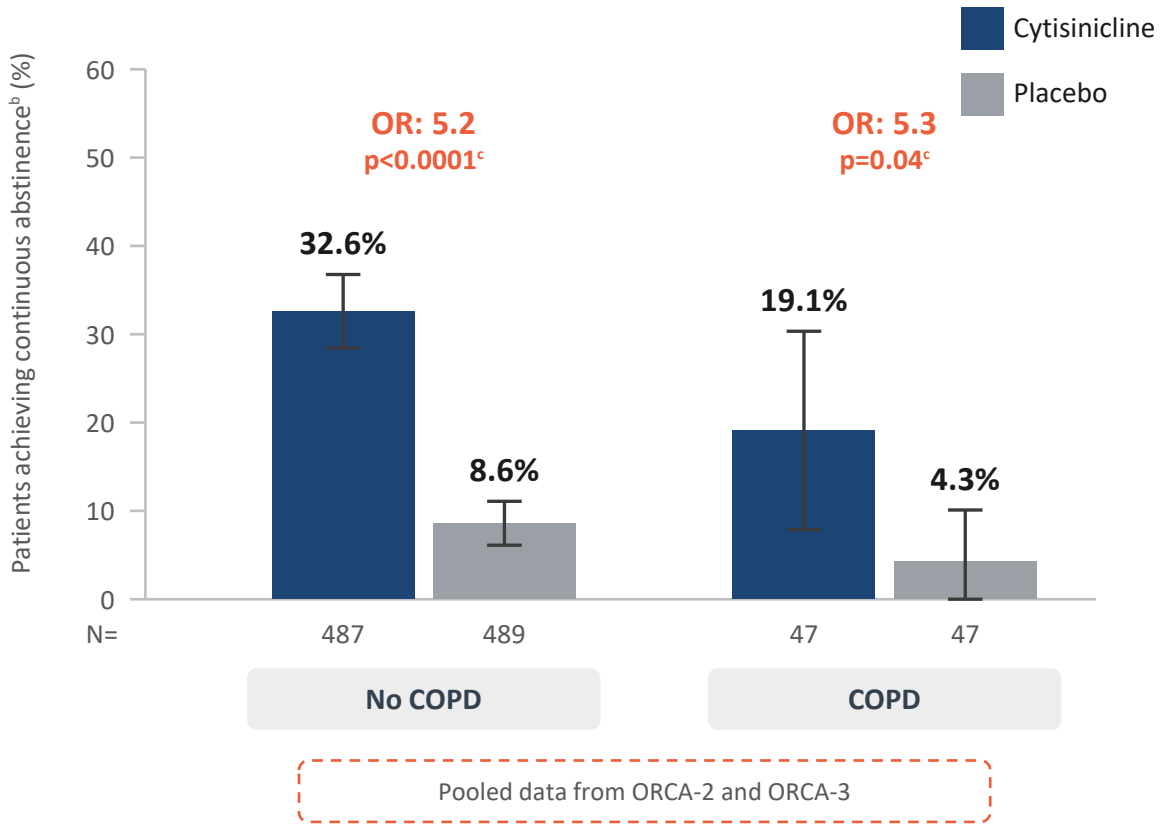
higher odds of cessation
with prior varenicline exposure

[1] Data presented at the Society for Research on Nicotine & Tobacco (SRNT) Annual Meeting, March 2026. https://achievelifesciences.com/products/resources/
[a] Continuous CO-verified smoking abstinence, Week 9-12; b P-value for difference in proportion, via Cochran-Mantel-Haenszel test; c vs placebo. Error bars represent 95% CI. CO, carbon monoxide; OR, odds ratio.

Potential efficacy in hard-to-treat populations, such as experienced smokers with COPD[1]

Thorax
AN INTERNATIONAL JOURNAL OF RESPIRATORY MEDICINE
Manuscript Published, 2025

Primary endpoint | **Continuous abstinence[a], weeks 9-12**



OVER

5-fold

higher odds of cessation

whether or not patients had COPD, a high unmet-need population

[1] Prochaska JJ, Rubinstein M, Perdok R, Blumenstein B, Jacobs C. Cytisinicline for smoking cessation in individuals with self-reported COPD: a post hoc analysis of the ORCA-2 and ORCA-3 trials. Thorax. 2025;81(2):164. https://thorax.bmj.com/content/81/2/164

[a] Continuous CO-verified smoking abstinence, Week 9-12; b P-value for difference in proportion, via Cochran-Mantel-Haenszel test; c vs placebo. Error bars represent 95% CI. CO, carbon monoxide; OR, odds ratio.

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Cytisinicline Efficacy in Hard-to-Treat Populations, Participants with a Baseline History of Cancer

ASCO Annual Meeting 2026
Abstract #e22676 • Publication Only

ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY

BACKGROUND

Post-hoc analysis of ORCA-2 and ORCA-3 Phase 3 RCTs evaluating cytisinicline vs placebo in the subset of participants reporting a cancer history at baseline.

n = 120 of 1,602 total participants

Mean age 60.6 yrs • Mean smoking duration 44.4 yrs

Top cancers: basal cell (n=31), breast (n=21), SCC (n=19)

EFFICACY RESULTS

6-WEEK TREATMENT (Wks 3–6)

24.4%

cytisinicline (11/45) vs 10.5% placebo (4/38)

OR 2.75 (95% CI 0.81–10.74)

12-WEEK TREATMENT (Wks 9–12)

32.4%

cytisinicline (12/37) vs 15.8% placebo (6/38)

OR 2.56 (95% CI 0.84–8.24)

SAFETY & TOLERABILITY

- Well tolerated; no serious treatment-related adverse events
- Most common TEAEs (≥5%): insomnia, abnormal dreams
- Discontinuation due to AEs: <3% across all treatment groups

CONCLUSION

Cytisinicline was well tolerated and showed numerically higher abstinence rates vs placebo in cancer survivors. Smoking cessation is an underutilized but highly modifiable determinant of cancer outcomes.

J Clin Oncol 44, 2026 (suppl 16; abstr e22676) • Post-hoc / exploratory analysis

Smoking cessation is associated with reduced mortality risk among cancer patients, even when initiated after diagnosis or in patients with advanced-stage disease

ORIGINAL RESEARCH

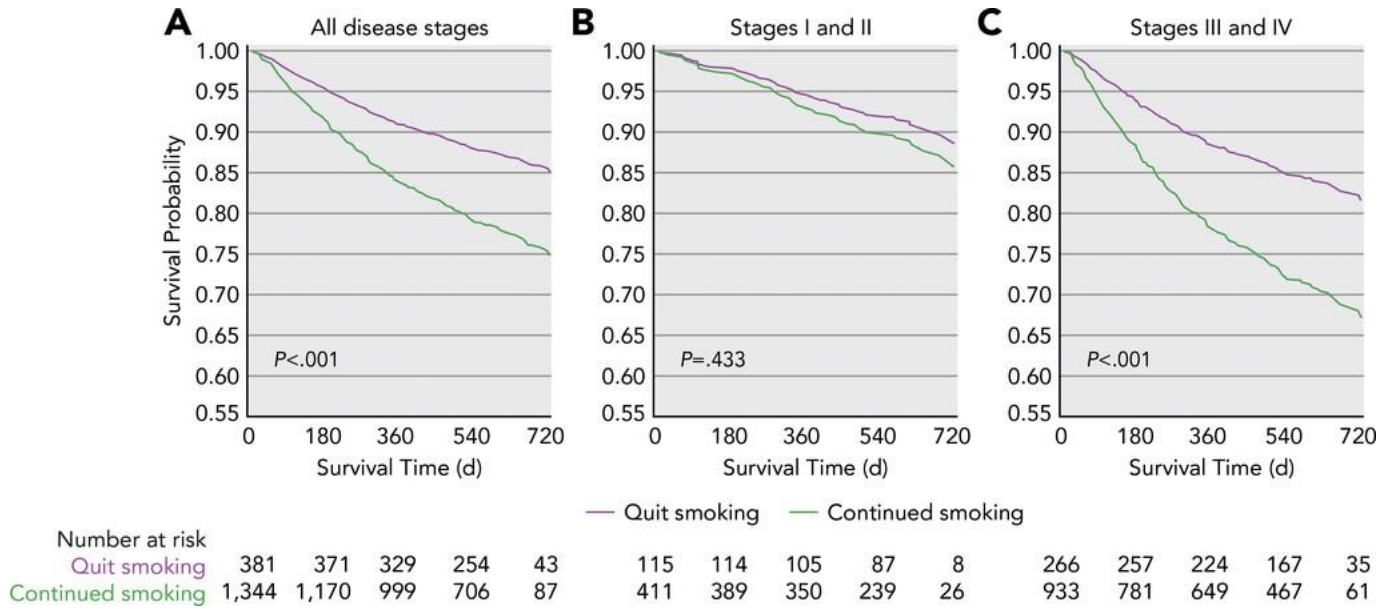
Smoking Cessation and Mortality Risk in Cancer Survivorship: Real-World Data From a National Cancer Institute–Designated Cancer Center

Steven Tohmasi, MD, MPHS[1,2]; Timothy B. Baker, PhD[3,4]; Brendan T. Heiden, MD, MBA, MPHS[2]; Jingling Chen, BS[5]; Nina Smock, BA[5]; Ethan J. Craig, MD, MPH[6]; Nicholas B. Griffith, MD[7]; James Reddy, BA[5]; Graham A. Colditz, MD, DrPH[1,8]; Ramaswamy Govindan, MD[8,9]; Laura J. Bierut, MD[5]; and Li-Shiun Chen, MD, MPH, ScD[5,8]

Abstract

Background: Although evidence-based tobacco cessation treatments are recommended for all patients with cancer who smoke, they are often underutilized in routine oncology care due to time and resource constraints and limited understanding of the impact of smoking cessation on long-term outcomes in patients with advanced-stage cancer. This study aimed to evaluate the association between smoking cessation and overall survival (OS) in cancer survivors who smoke, across all disease stages. **Methods:** We conducted an observational cohort study of 13,282 patients diagnosed with cancer who were evaluated in our outpatient oncology clinics between June and December 2018. Patients who smoked were prospectively followed to evaluate smoking cessation rates over the following 6 months. We assessed the impact of index-visit smoking status and smoking cessation within 6 months on 2-year OS using multivariable Cox proportional hazards models and the Kaplan-Meier method. **Results:** Compared with patients who never smoked (n=6,568; 49.5%), those who reported currently smoking (n=1,725; 13.0%) (adjusted hazard ratio for death [aHR], 1.35; CI, 1.20–1.53) or having previously smoked (n=4,989; 37.6%) (aHR, 1.13; CI, 1.03–1.25) at their index visit had increased risk of all-cause mortality. Only 22.1% (n=381) of patients who reported currently smoking at their index visit quit smoking within 6 months. In multivariable analyses, patients who continued to smoke had a higher risk of all-cause mortality (aHR, 1.97; CI, 1.53–2.55) compared with those who had quit smoking. Subgroup analyses by cancer stage revealed an association between continued smoking and all-cause mortality in patients with advanced-stage (III or IV) cancer (aHR, 2.11; 95% CI, 1.60–2.79). **Conclusions:** Postdiagnosis smoking cessation is associated with improved OS in cancer survivors, including those with advanced-stage cancer. Smoking cessation support should be provided to all cancer survivors who smoke, irrespective of cancer type or stage. Promoting smoking cessation in oncology care settings via systematic implementation efforts may aid in reducing smoking and mortality rates.

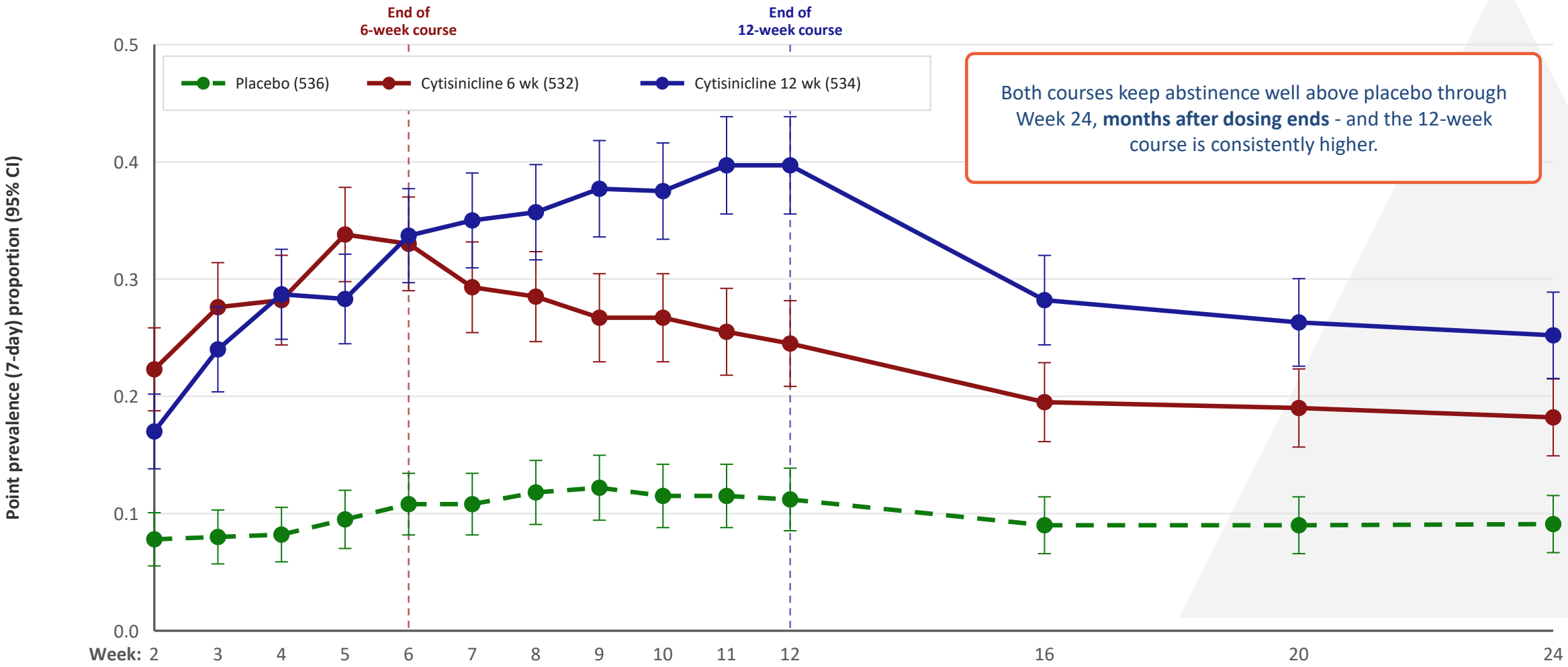
J Natl Compr Canc Netw 2025;23(10):e257059
doi:10.6004/jnccn.2025.7059



Tohmasi S, Baker TB, Heiden BT, et al. *Smoking Cessation and Mortality Risk in Cancer Survivorship: Real-World Data From a National Cancer Institute-Designated Cancer Center.* J Natl Compr Canc Netw. 2025;23(10):e257059. doi:10.6004/jnccn.2025.7059

Dosing is a short, fixed course of 6 or 12 weeks

Pooled point-prevalence abstinence is sustained through Week 24, with the 12-week course outperforming 6 weeks



Both courses keep abstinence well above placebo through Week 24, **months after dosing ends** - and the 12-week course is consistently higher.

Pooled point-prevalence abstinence (7-day) from the ORCA-2 and ORCA-3 Phase 3 trials (N=1068 placebo + 6-week; N=1070 placebo + 12-week). Error bars represent 95% CI. Cytisinicline dosing periods: 6 or 12 weeks; assessments continued through Week 24.

For two consecutive years, the FDA recognized cytisinicline as a national priority treatment for vaping cessation

2024
FDA RECOGNITION

Breakthrough Therapy Designation[1]

- Reserved for therapies showing the potential for substantial improvement over existing options
- Enables expedited development and intensive FDA guidance

2025
FDA RECOGNITION

Commissioner's National Priority Voucher[2]

- New program to accelerate review of treatments addressing major public-health priorities
- Cytisinicline chosen among the first nine sponsors in the program

[1] Achieve Life Sciences. Press release. July 31, 2024. ir.achievelifesciences.com/news-events/press-releases
[2] US Food and Drug Administration. Press release, October 16, 2025. fda.gov/news-events/press-announcements/fda-awards-first-ever-national-priority-vouchers-nine-sponsors

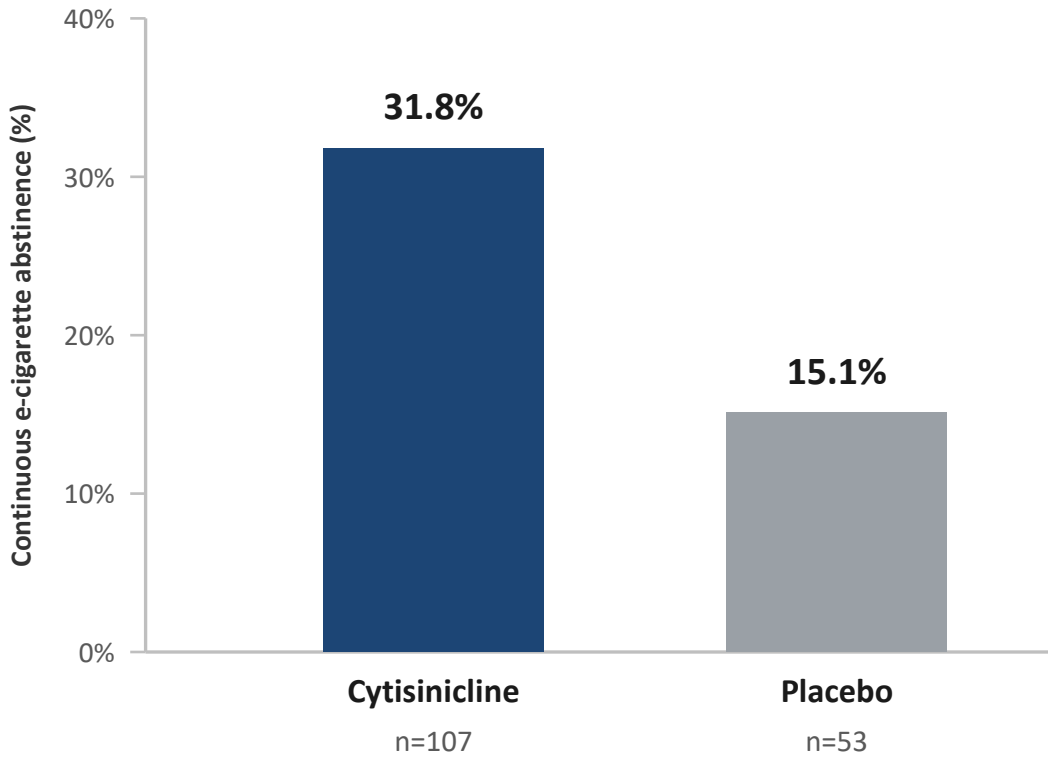
Research

JAMA Internal Medicine | Original Investigation

Cytisinicline for Vaping Cessation in Adults Using Nicotine E-Cigarettes
The ORCA-V1 Randomized Clinical Trial

Nancy A. Rigotti, MD; Neal L. Benowitz, MD; Judith J. Prochaska, PhD, MPH; Daniel F. Cain, BSc; Julie Ball, MS; Anthony Clarke, PhD; Brent A. Blumenstein, PhD; Cindy Jacobs, PhD, MD

JAMA Internal Medicine



Primary Outcome

End of treatment (Weeks 9-12)

OR 2.64

95% CI 1.06-7.10 P=0.035

Rigotti NA, Benowitz NL, Prochaska JJ, et al. Cytisinicline for vaping cessation in adults using nicotine e-cigarettes: the ORCA-V1 (Phase 2) randomized clinical trial. JAMA Intern Med. 2024;184:922. doi:10.1001/jamainternmed.2024.1313. Endpoint: biochemically verified continuous e-cigarette abstinence, Weeks 9-12.

Current FDA-approved options present significant tolerability and adherence challenges

Varenicline

(Chantix)

TOLERABILITY & LABEL WARNINGS

- **4.4×** the odds of nausea vs placebo; nausea in ~30% of patients[1,2,3]
- Higher odds of any adverse event (1.8×) and treatment discontinuation[1]
- Carried an FDA boxed warning for neuropsychiatric events (2009-2016); brand recalled in 2021 (nitrosamines)[3]

Bupropion

(Zyban)

LIMITED EFFICACY

- Less effective for quitting than varenicline[2]
- Seizure risk; contraindicated in seizure or eating disorders[4]
- Multiple drug interactions, inhibits CYP2D6, raising levels of many antidepressants, antipsychotics and beta blockers[4]
- Insomnia and dry mouth are common[4]

NRT

Nicotine replacement therapy

DOSING & ADHERENCE

- Frequent, multiple-daily dosing limits real-world adherence[5]
- Modest efficacy versus prescription options[2,5]
- Each formulation (patch, gum, lozenge) carries its own tolerability issues[5]

[1] Drovandi AD, et al. Curr Drug Saf. 2016;11(1):78-85.
[2] Anthenelli RM, et al. (EAGLES) Lancet. 2016;387:2507-2520.
[3] CHANTIX (varenicline) labeling: FDA boxed warning for neuropsychiatric events added 2009, removed Dec 2016 (EAGLES); brand Chantix recalled 2021 (N-nitroso-varenicline impurities). https://labeling.pfizer.com/ShowLabeling.aspx?id=557
[4] Zyban (bupropion) Prescribing Information, GlaxoSmithKline, 3/2021. [5] Choi H. Cleveland Clinic J Med. 2021;88(7):393-404.

Cytisinicline was generally well tolerated with low incidence of discontinuation due to treatment-emergent adverse events (TEAEs)

<5% of patients on cytisinicline discontinued due to adverse events

	Low incidence of TEAEs observed, most of which were mild or moderate	Overall Placebo (N=636)	Overall Cytisinicline (N=1534)
>5% TEAEs Type	At least 1 TEAE	383 (60.2)	1011 (65.9)
	Insomnia	35 (5.5)	167 (10.9)
	Abnormal dreams	25 (3.9)	152 (9.9)
	Nausea	50 (7.9)	103 (6.7)
	Headache	45 (7.1)	128 (8.3)
	At least 1 treatment-related TEAE	171 (26.9)	595 (38.8)
	At least 1 serious TEAE	11 (1.7)	61 (4.0)
	At least 1 treatment-related serious TEAE	0	1 (0.1)
Discontinuation Rates	At least 1 TEAE leading to discontinuation	15 (2.4)	67 (4.4)
	At least 1 treatment-related TEAE leading to discontinuation	7 (1.1)	48 (3.1)

Reference: **1.** ORCA-2 & ORCA-3 pooled safety data. ORCA-OL interim safety analysis. Data on File Achieve Life Sciences, Inc

Nicotine & Tobacco Research, 2026, **00**, 1–3
https://doi.org/10.1093/ntr/ntag039
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Brief Report

SRNT OXFORD

Receptor selectivity of cytisinicline: minimal 5-HT3 binding may explain lower incidence of nausea in smoking cessation therapy

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- Unlike varenicline, cytisinicline shows near-complete binding at the α4β2 nicotinic receptor (99% displacement) but no meaningful binding at the 5-HT3 receptor (−8%) - the receptor implicated in nausea
- This selective receptor profile provides a pharmacologic rationale for cytisinicline's lower nausea rates in clinical trials, supporting its potential as a better-tolerated alternative for patients who cannot tolerate current cessation therapies

Minimal off-target activity may support a favorable safety profile

5-HT3 is a receptor commonly associated with nausea and vomiting

NICOTINE & TOBACCO RESEARCH

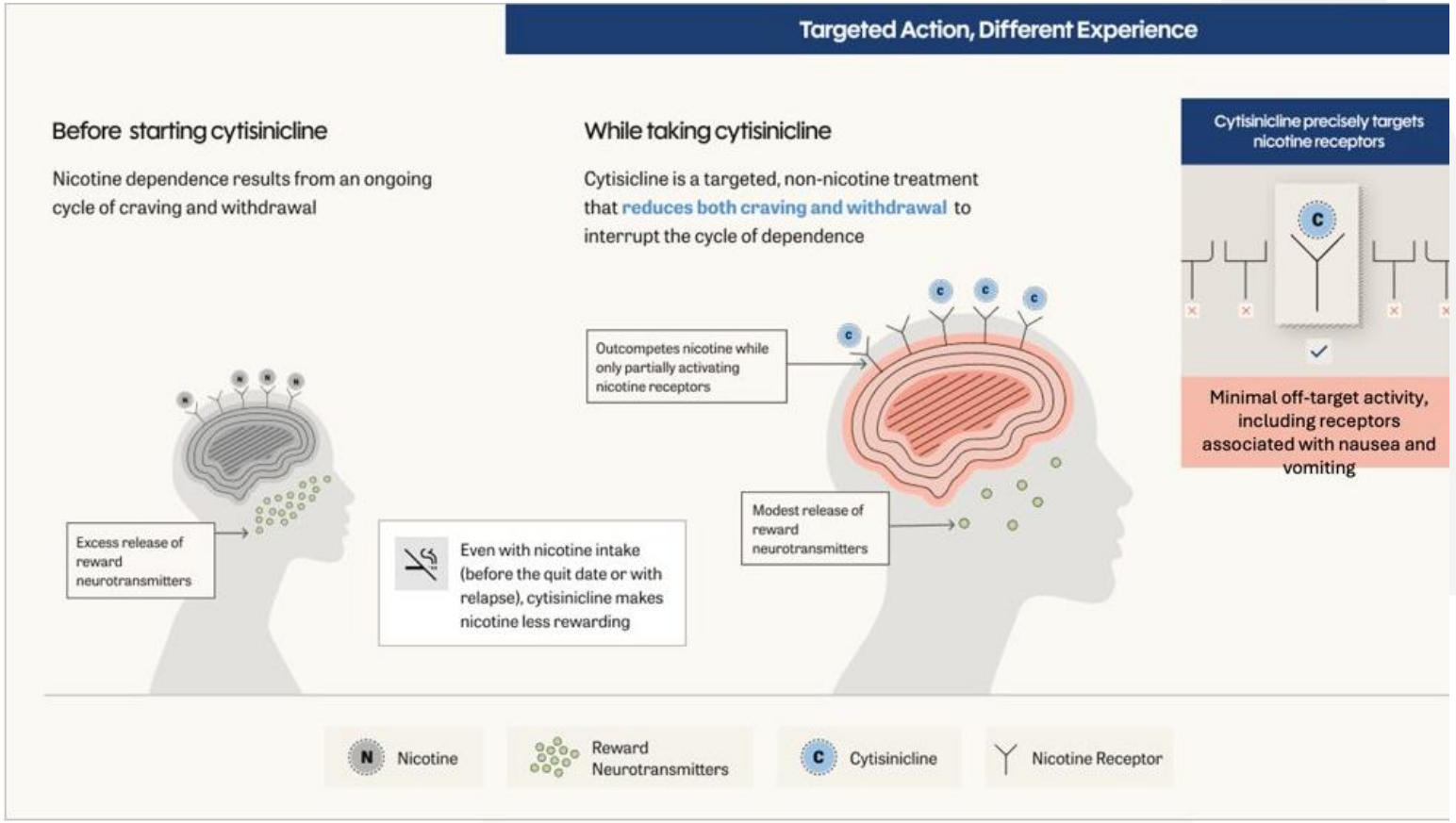
Receptor Selectivity of Cytisinicline: Minimal 5-HT3 Binding May Explain Lower Incidence of Nausea in Smoking Cessation Therapy
Mark L. Rubinstein, MD; Cindy Jacobs, PhD, MD | https://academic.oup.com/ntr/article-lookup/doi/10.1093/ntr/ntag039

RECEPTOR BINDING (TABLE 1)

Binding assay[a]	% Displacement
Nicotinic acetylcholine α4β2 *On-target receptor*	**99**
Serotonin (5-HT3) *Off-target — linked to nausea*	**–8**

[a] Human; 10 µM. Significant response ≥ 50% inhibition of specific binding.

Cytisinicline shows essentially no 5-HT3 binding (–8%), consistent with its favorable tolerability versus other cessation agents



52-week continuous therapy shows persistent tolerability and a favorable safety profile

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Cytisinicline for cigarette smoking and e-cigarette vaping cessation: Long-term safety data from the ORCA-OL clinical trial

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Digital poster available via QR code

Poster: #325

Introduction

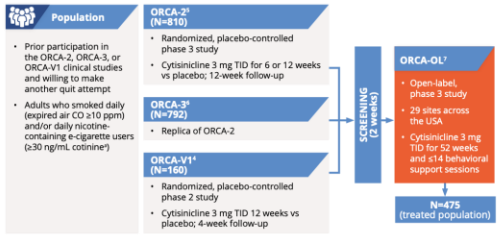
- Approximately 25 million adults in the USA smoke,[1] and no new FDA-approved smoking cessation therapies have been introduced since 2006[2]
- Approximately 18 million adults in the USA use electronic (e)-cigarettes,[3] with no FDA-approved treatments indicated specifically as an aid to nicotine e-cigarette cessation
- Cytisinicline is a plant-based alkaloid and partial agonist at α4β2 nicotinic acetylcholine receptors[4]
- A novel cytisinicline treatment regimen, consisting of a 3 mg tablet administered three times daily (TID) for 6 or 12 weeks, is currently under regulatory review
- In the phase 3 ORCA-2 and ORCA-3 trials, cytisinicline was more effective than placebo in achieving continuous smoking abstinence in adults, and in the phase 2 ORCA-V1 trial it was also more effective in achieving continuous abstinence from e-cigarettes, and was well tolerated across all studies[4–6]
- Adult participants from the ORCA-2, ORCA-3, or ORCA-V1 trials who agreed to make another quit attempt were enrolled in a 52-week open-label (OL) safety trial: **ORCA-OL**[7]

Objective

To evaluate the long-term safety of cytisinicline in adults who smoke/vape who had previously participated in the ORCA-2, ORCA-3, or ORCA-V1 studies[4–6]

Materials and methods

Figure 1. Study design



[a]Using a point-of-care cotinine oral fluid screening device if self-reporting as users of nicotine-containing e-cigarettes.
CO, carbon monoxide; e-cigarettes, electronic cigarettes; OL, open label; ppm, parts per million; TID, three times daily.

Assessments

- Treatment-emergent adverse event (TEAE) incidence was assessed, including serious adverse events (SAEs), severity (mild, moderate, severe), and events leading to dose reduction, interruption, or discontinuation

Results

Table 1. Baseline characteristics

Characteristic	Participants (N=475)
Female, n (%)	**275 (57.9)**
Age, median years (min, max)	**55 (22, 79)**
Race, n (%)[a]	
White	**386 (81.3)**
Black or African American	**79 (16.6)**
User type, n (%)	
Current smoker	**402 (84.6)**
Current e-cigarette user	**61 (12.8)**
Dual user	**12 (2.5)**
Cigarette intake per day in past 30 days, median	**20**
Vaping product intake days in past 30 days, median	**30**

[a]Other race categories (n [%]) were: American Indian or Alaska Native (3 [0.6%]), Asian (3 [0.6%]), and Other (4 [0.8%]).
e-cigarette, electronic cigarette.

Table 2. Cytisinicline exposure

Exposure parameter	Participants (N=475)
Median cumulative duration of cytisinicline exposure,[a] days	**361**
Participants with cytisinicline exposure,[a] n (%)	
≥24 weeks duration	**392 (82.5)**
≥48 weeks duration	**319 (67.2)**
≥51 weeks duration	**281 (59.2)**

[a]Number of days where the participant received ≥1 dose of cytisinicline.

Long-term safety

No new safety signals were identified on independent Data Safety Monitoring Committee (DSMC) review

- Overall, 315 (66.3%) participants reported ≥1 TEAE over the 52-week treatment period
- Most TEAEs (94.8%) were mild or moderate in intensity
- Serious TEAEs occurred in 31 participants (6.5%)
- Two deaths (0.4%) occurred and were considered unrelated to treatment, in the context of underlying medical conditions
- TEAEs that occurred in ≥5.0% of participants included abnormal dreams (8.4%), insomnia (8.4%), and upper respiratory tract infection (6.7%) **(Table 3)**

Table 3. Summary of most commonly reported TEAEs

TEAEs reported in ≥5.0% of participants	Participants (N=475)
≥1 TEAE, n (%)	**315 (66.3)**
Abnormal dreams	**40 (8.4)**
Insomnia	**40 (8.4)**
Upper respiratory tract infection	**32 (6.7)**

TEAE, treatment-emergent adverse event.

Nausea, a common TEAE reported with other smoking cessation treatments, was reported in 12 participants (2.5%)

- 42 participants (8.8%) experienced ≥1 TEAE leading to dose reduction or interruption during the study **(Table 4)**
- TEAEs led to study discontinuation in 27 participants (5.7%); no individual TEAE leading to discontinuation occurred in ≥1% of participants

Table 4. Summary of TEAEs leading to dose reduction, interruption, or discontinuation

TEAEs reported in ≥1.0% of participants	Participants (N=475)
≥1 TEAE leading to dose reduction or interruption, n (%)	**42 (8.8)**
Abnormal dreams	**7 (1.5)**
Insomnia	**6 (1.3)**
≥1 TEAE leading to discontinuation, n (%)	**27 (5.7)**

TEAE, treatment-emergent adverse event.

Conclusions

- No new safety signals identified per independent DSMC review; cytisinicline 3 mg TID was generally well tolerated over 52 weeks in adults who smoke and/or use e-cigarettes who were attempting to quit
- Nausea was infrequently reported (2.5%) among participants receiving cytisinicline
- Overall, few participants (5.7%) discontinued due to TEAEs
- Taken together with previous studies, these findings further support cytisinicline as a well-tolerated treatment option for cigarette smoking and e-cigarette vaping cessation

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Disclosures: This research was funded by Achieve Life Sciences. 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. NAR has received grant funding from Achieve Life Sciences. RP, MLR, and ML-A are employees of Achieve Life Sciences.

References: **1**. National Center for Health Statistics. National Health Interview Survey, 2023 and 2024. 2026. Available at: https://www.cdc.gov/nchs/nhis.htm; **2**. Foulds J et al. JAMA. 2023;330:129–30; **3**. Vahratian A et al. NCHS Data Brief, no 524. Hyattsville, MD: National Center for Health Statistics. 2025. Available at: https://dx.doi.org/10.15620/cdc/174583; **4**. Rigotti NA et al. JAMA Intern Med. 2024;184:922–30; **5**. Rigotti NA et al. JAMA. 2023;330:152–60; **6**. Rigotti NA et al. JAMA Intern Med. 2025;185:648–55; **7**. Available at: https://clinicaltrials.gov/study/NCT06435221.

Poster presented at the American Thoracic Society (ATS) Annual Meeting, May 15–20, 2026, Orlando, FL, USA

Matching-adjusted indirect comparison: cytisinicline vs varenicline

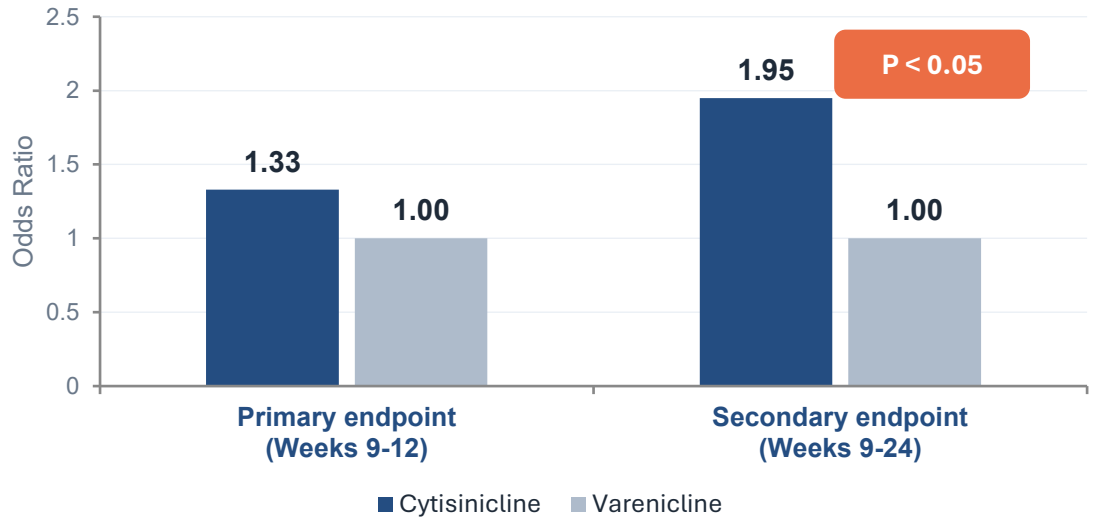
Higher odds of quitting vs varenicline at the secondary (weeks 9-24) endpoint;
Lower odds of nausea vs varenicline

Journal of Health Economics and Outcomes Research

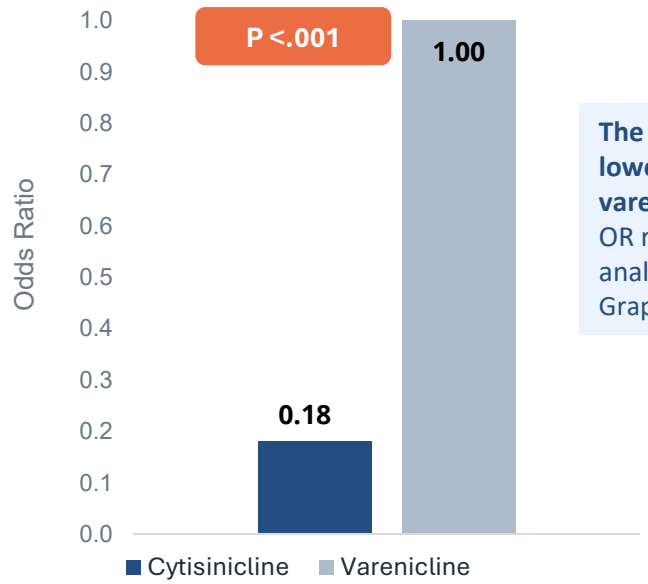
ATS 2026

A matching-adjusted indirect treatment comparison (MAIC) was conducted to estimate **relative efficacy and tolerability between cytisinicline and varenicline**, given there is no direct head-to-head clinical trial.

Cytisinicline odds of quitting compared to varenicline through 24 weeks



Cytisinicline odds of nausea compared to varenicline



The odds of nausea were 82–87% lower with cytisinicline than varenicline.
OR range: 0.13-0.18 across all analyses.
Graph depicts highest OR within range.

1. Rubinstein M et al. Comparative Effectiveness of Cytisinicline and Varenicline for Smoking Cessation: A Matching-Adjusted Indirect Comparison (MAIC). Draft manuscript. Source: JHEOR; presented at ATS 2026.

Disclaimer: Results are based on an indirect comparison using Matching-Adjusted Indirect Comparison (MAIC) methodology. These findings are exploratory, derived from separate trials differing in design, population, and outcome measures, and should be interpreted cautiously; they are not conclusive evidence of comparative efficacy or safety. **Methods:** Pooled patient-level data from cytisinicline trials (ORCA-2/3) reweighted to match baseline characteristics of the varenicline trial (EAGLES), Weighting based on pre-specified effect modifiers identified from the EAGLES varenicline cohort, Multiple scenarios tested, varying both the EAGLES comparator subgroup and the treatment effect modifiers, Unadjusted indirect comparisons also conducted to evaluate robustness and quantify uncertainty

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Multiple value drivers designed to de-risk potential approval

01

Large, underserved market

~38M U.S. smokers, vapers or both, with no new smoking-cessation therapy approved in over two decades and **zero** approved options for vaping cessation.

02

Strong efficacy

Up to **5-6x** higher odds of quitting vs. placebo across Phase 3 trials, with benefit shown in subgroups (COPD, oncology, and high numbers of prior quit attempts).

03

Favorable safety profile

Minimal **5-HT3** receptor binding is potentially associated with lower nausea rates than other therapies

04

Clear regulatory path

NDA accepted and backed by **1,500+** participants exposed to cytisinicline; safety data in **400+** participants at 6+ months and **200+** at 1 year.

05

Resourced for launch

Up to **$354M** in financing and experienced commercial team with launch experience position Achieve to execute from day one.

A large unmet market, differentiated Phase 3 efficacy and tolerability, a clear path to approval, and a proven team funded into launch.

See preceding slides for full data, sources, and disclaimers.

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July 2026