Achieve Rx

The Quit Company.

# Quitting deserves medicine. We're developing it.

NASDAQ: QUIT

# 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., DBA AchieveRx ("AchieveRx," "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. Certain data in this presentation are from post hoc, subgroup or exploratory analyses or from open-label, single-arm studies without a comparator; these analyses are hypothesis-generating and should be interpreted with caution. Cytisinicline is an investigational product candidate and has not been approved by the FDA. Its safety and efficacy has not been established.

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After two decades without a new medicine to help people quit smoking, we are developing

# Cytisinicline

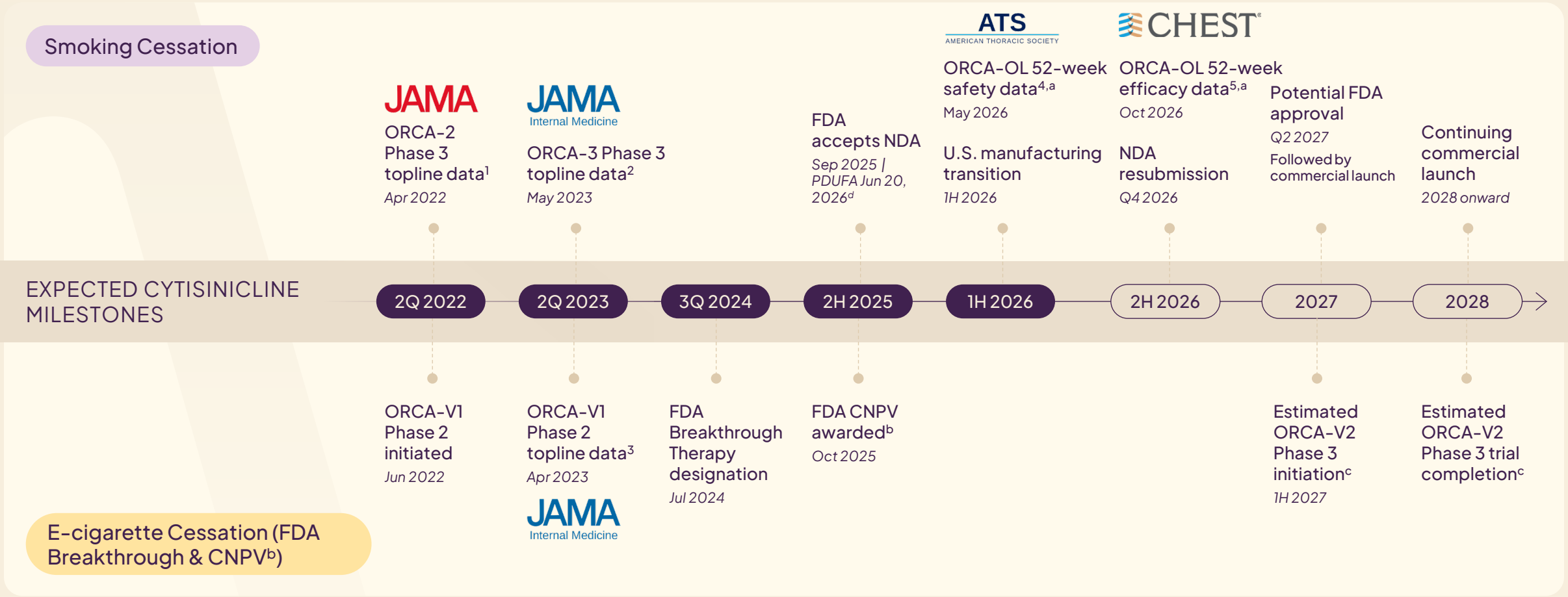
an investigational compound that binds to nicotinic receptors

which demonstrated increased odds of quitting in two randomized trials, including in hard-to-treat patients, and was generally well tolerated in all three Phase 3 trials.[1]

1. ORCA-2: Rigotti NA, et al. JAMA. 2023;330(2):152-160. ORCA-3: Rigotti NA, et al. JAMA Intern Med. 2025;185(6):648-655. ORCA-OL: Rubinstein ML, et al. Late-breaking abstract and rapid oral presentation, CHEST 2026 Annual Meeting (NCT06435221).

# 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.
5. ORCA-OL 52-week efficacy data: late-breaking abstract and rapid oral presentation, CHEST 2026 Annual Meeting, October 2026. Rubinstein ML, et al. (NCT06435221). a. ORCA-OL enrolled people who smoke and people who vape; every participant was still smoking or vaping after a prior ORCA trial.
6. Achieve Life Sciences. Achieve Life Sciences Receives Complete Response Letter from FDA for Cytisinicline NDA. Press release, June 22, 2026. https://ir.achieverx.com/news-events/press-releases/detail/264/achieve-life-sciences-receives-complete-response-letter-from-fda-for-cytisinicline-nda

Timeline reflects current management expectations, which are subject to change and are not guarantees of future results. b. Commissioner's National Priority Voucher (CNPV). c. ORCA-V2 e-cigarette cessation program timeline is best estimate. d. Complete Response Letter received Q2 2026, citing a prior third-party manufacturing facility; no efficacy or clinical safety deficiencies identified.[6]

# Well-capitalized, with an experienced management team

UP TO

**$354M**

in total financing[1]

Upfront

**$180M**

Milestone-driven warrants

**$174M**

Exercisable now, expire within 20 days of FDA approval.

**$201.5M**

cash, cash equivalents, and marketable securities as of September 30, 2026[2]

LED BY

Frazier Life Sciences | TPG Life Sciences Innovations | venBio Partners | Paradigm BioCapital Advisors | Marshall Wace

PARTICIPANTS

Janus Henderson | Wellington | Venrock | Vivo

## Management team[3]

**Andrew D. Goldberg, MD**
**Chief Executive Officer.** Physician, healthcare investor (Vivo Capital, Marshall Wace), and governance leader; director or observer at 19 life sciences companies, including Tarsus and Elektrofi; lead investor in Verona Pharma and Harmony Biosciences. Dual board-certified in critical care and emergency medicine; academic appointment at Mayo Clinic.

**Mark L. Rubinstein, MD**
**Chief Medical Officer.** Internal medicine and adolescent medicine physician; Professor Emeritus of Pediatrics, UCSF.

**Benjamin Halladay**
**Chief Financial Officer.** Previously Chief Financial Officer of Esperion Therapeutics through its sale to ARCHIMED; earlier at Pfizer.

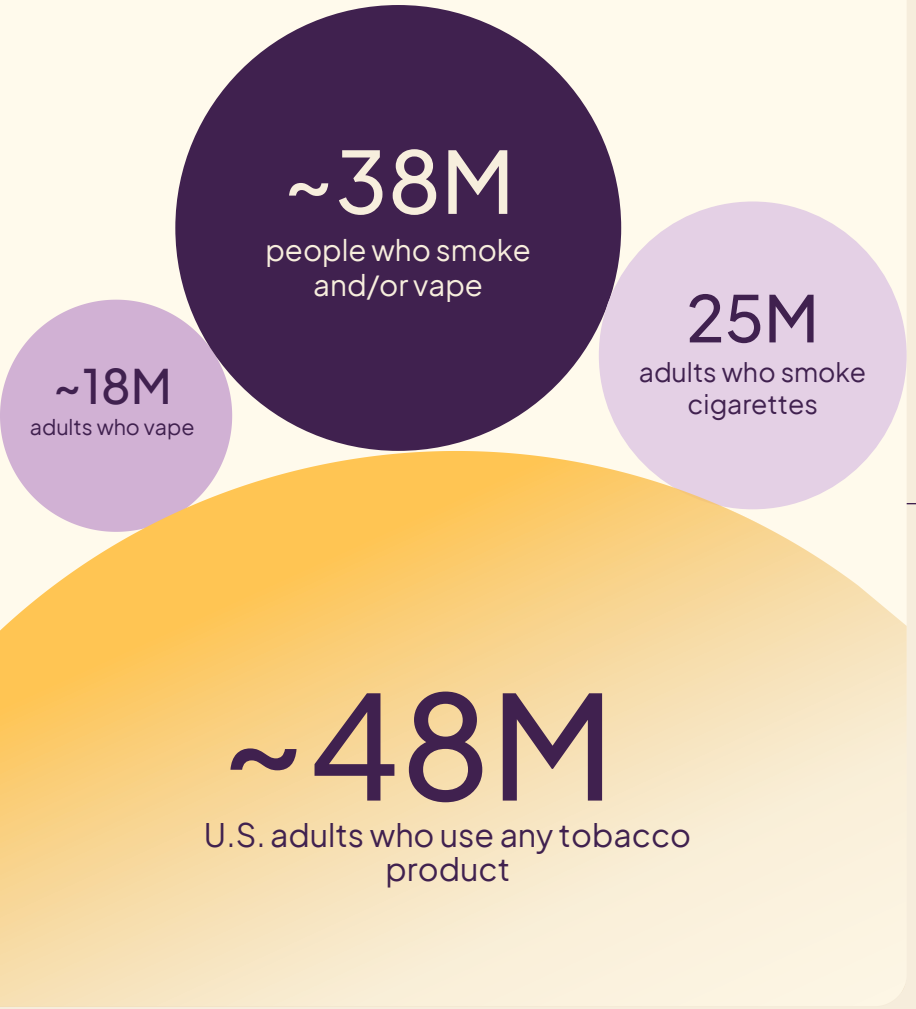
**Mark Zappia**
**Senior Vice President, Commercial.** Previously Vice President, Commercial Operations at Verona Pharma through the Ohtuvayre launch.

**Erik Atkisson**
**Chief Legal Officer.** More than 25 years of biopharma legal leadership; previously General Counsel at Eiger BioPharmaceuticals and Chief Compliance Officer at Cytokinetics.

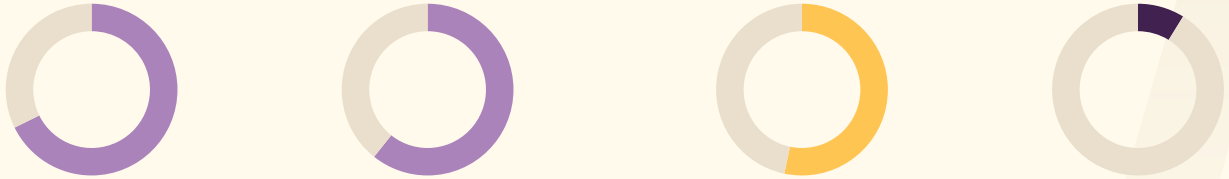
1. Achieve Life Sciences. Press release, June 2026 (financing). 2. AchieveRx. Third Quarter 2026 Financial Results and Business Updates. Press release, November 10, 2026. 3. Achieve Life Sciences. Press release, April 16, 2026 (CEO appointment); AchieveRx. Leadership. achieverx.com/about/leadership.

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

## A LARGE POPULATION[1]




## MOST PLAN TO QUIT. FEW DO



**67.7%** of adults who smoke want to quit[2]

**60.7%** of adults who vape plan to quit[3]

**53.3%** of adults who smoke try to quit each year[2]

**8.8%** of adults who smoke quit each year[2]

## ONLY ABOUT 1 IN 6 USES A PRESCRIPTION MEDICINE[4]




Prescription: varenicline ~8%, bupropion ~5%, and prescription NRT ~4%[5]

**2006** newest medicine approved to help people quit smoking[6]

**None** approved to help people quit vaping[7]


1. Agaku I. Tobacco Product Use among U.S. Adults, 2023–2024. NEJM Evidence. 2026. doi:10.1056/EVIDpha2500339. ~38M derived as 25.2M who smoke + 17.8M who vape (2024) minus ~4.5M who do both (2023; Arrazola RA, et al. MMWR Morb Mortal Wkly Rep. 2025;74:118-121).
2. CDC. Smoking Cessation: Fast Facts. National Health Interview Survey, 2022.
3. Palmer AM, et al. Interest in quitting e-cigarettes among adult e-cigarette users with and without cigarette smoking history. JAMA Netw Open. 2021;4(4):e214146.
4. Achieve Life Sciences, data on file: analysis of CDC National Health Interview Survey, 2024, and Komodo Health claims, 2023–2025.
5. Trinity Life Sciences analysis commissioned by Achieve Life Sciences (prescription split by product).
6. U.S. Public Health Service, Office of the Surgeon General. Smoking Cessation: A Report of the Surgeon General. Washington, DC: HHS; 2020.
7. U.S. Food and Drug Administration. Drugs@FDA.

# Nicotine dependence is a costly and growing medical problem

## SMOKING'S TOLL IN LIVES

**480K+**
U.S. deaths each year, the #1 cause of preventable death[1]

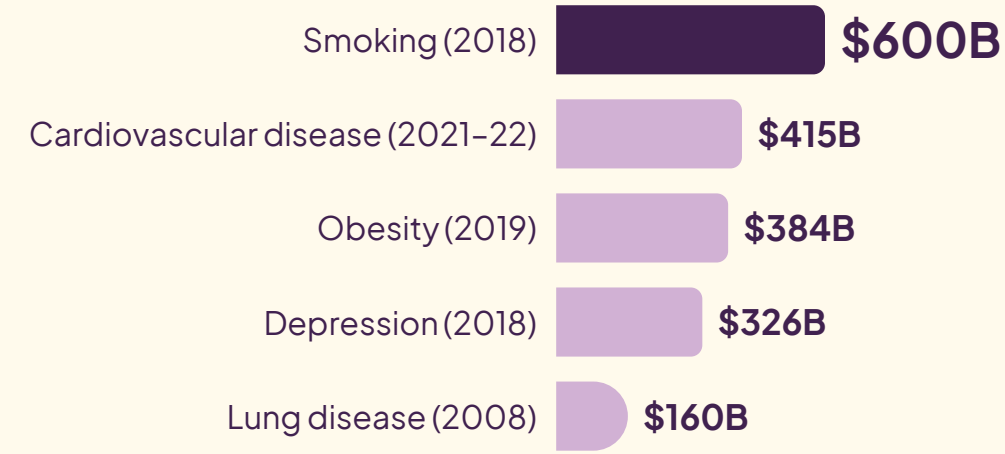
**~1 in 4**
of heart disease deaths[2]

**~1 in 3**
of cancer deaths[2]

More deaths than stroke, COPD, and diabetes combined[1,3]

## SMOKING'S TOLL IN DOLLARS

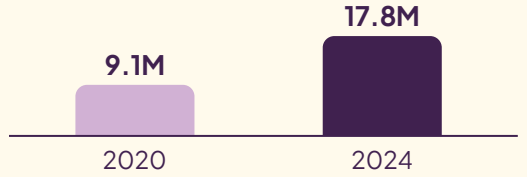
Annual U.S. economic cost: medical care plus lost productivity[4]




Smoking's total includes ~$240B in direct health care, and smoking also drives part of the cardiovascular cost.

## VAPING: A RISING PUBLIC HEALTH CRISIS

**~90%** growth in U.S. adult vaping, 2020–2024[5]




**~1 in 7**

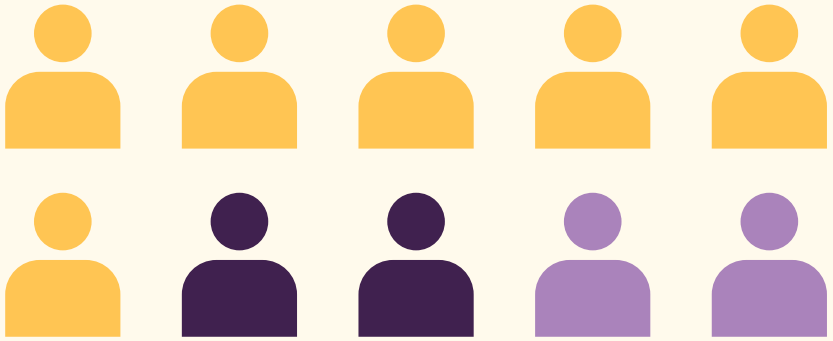


U.S. adults aged 18–34 vape, with 21–24 being the highest rate of any age group (15.5%)[6,7]


1. U.S. Department of Health and Human Services. The Health Consequences of Smoking: 50 Years of Progress. A Report of the Surgeon General. Atlanta, GA: CDC; 2014.
2. CDC. Tips From Former Smokers: Frequently Asked Questions. CDC. Health Effects of Cigarettes: Cancer.
3. National Center for Health Statistics. FastStats: Leading Causes of Death (2024 data).
4. CDC. Economic Trends in Tobacco. Palaniappan LP, et al. Circulation. 2026;153(9):e275-e906. Society of Actuaries Research Institute. Obesity Trends and the Impact on Morbidity and Mortality Costs. 2021. Greenberg PE, et al. PharmacoEconomics. 2021;39(6):653-665. National Heart, Lung, and Blood Institute. Fact Book, Fiscal Year 2008 (lung diseases). Estimates as published; not adjusted for inflation; conditions overlap.
5. Cornelius ME, et al. Tobacco Product Use Among Adults - United States, 2020. MMWR Morb Mortal Wkly Rep. 2022;71(11):397-405. Agaku I. Tobacco Product Use among U.S. Adults, 2023–2024. NEJM Evidence. 2026. doi:10.1056/EVIDpha2500339.
6. 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.html.
7. National Center for Health Statistics. NCHS Data Brief No. 524. January 2025.

# Many people who smoke see a specialist, with the highest density in pulmonology and cardiology offices[1]

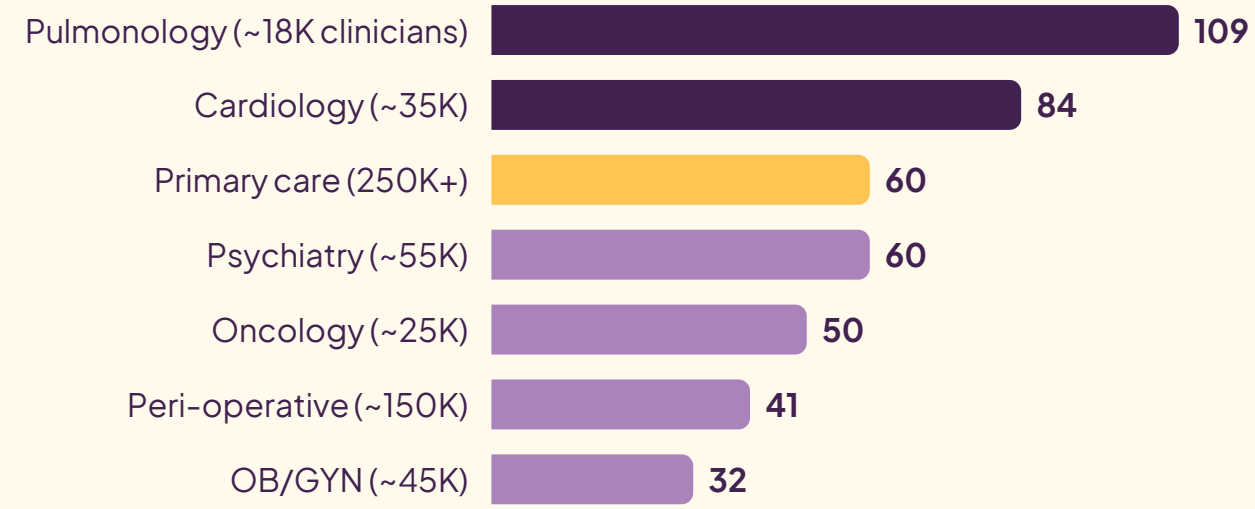
## WHERE ADULTS WHO SMOKE ARE SEEN[1,2]



**About 4 in 10** visits are to specialists (41.3%)

- **Comorbidity-driven (25.4%):** pulmonology, cardiology, psychiatry
- **Event-driven (15.9%):** oncology, peri-operative, OB/GYN
- **Primary care (58.7%):** physicians, NPs, and PAs

## ADULTS WHO SMOKE SEEN PER CLINICIAN




**Pulmonologists see nearly twice as many adults who smoke as primary care clinicians (109 vs 60), and cardiologists see 84.**

1. Achieve Life Sciences, data on file: analysis of Komodo Health claims, 2023–2025. Shares are of visits by claims-identified adults who smoke; per-clinician figures are 3-year rolling averages; clinician counts are rounded estimates by specialty of record, including NPs and PAs.
2. Trinity HCP attitude and usage research, commissioned by Achieve Life Sciences, 2026 (specialist segment definitions).

# 12 weeks of cytisinicline showed high odds of quitting smoking in pooled Phase 3 trials[1,2]

INDIVIDUAL STUDIES PUBLISHED

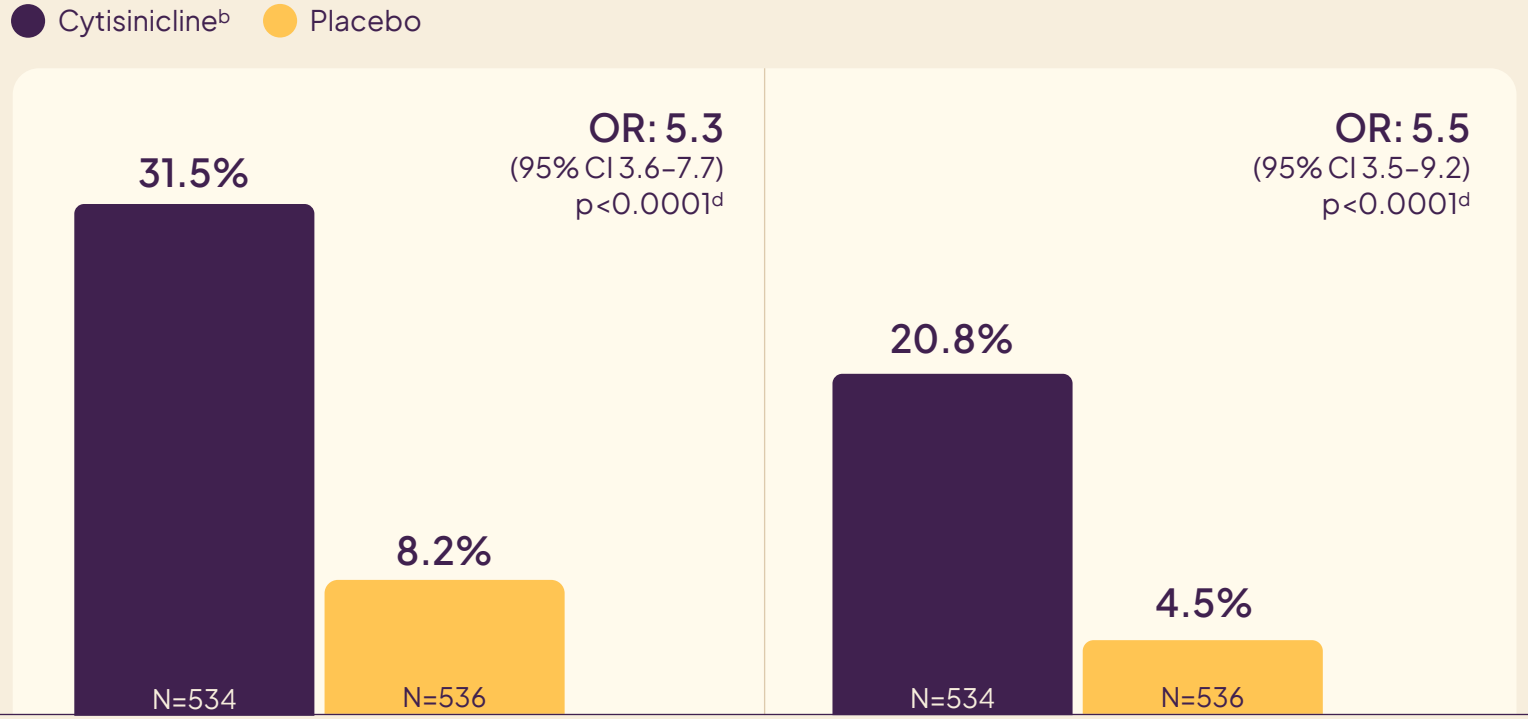
JAMA
JAMA
Internal Medicine

POOLED PRIMARY ENDPOINT[3]

## Continuous abstinence[a], weeks 9–12

POOLED SECONDARY ENDPOINT[3]

## Continuous abstinence[c], weeks 9–24




OVER

# 5-fold

higher odds of quitting vs placebo in pooled Phase 3 trials[3]

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. 3. Data on file, Achieve Life Sciences: pooled ORCA-2 and ORCA-3.
a. Continuous CO-verified abstinence, weeks 9–12; b. Cytisinicline 3 mg TID; c. Continuous CO-verified abstinence, weeks 9–24; d. P-value via Cochran-Mantel-Haenszel test. CI, confidence interval; CO, carbon monoxide; OR, odds ratio; TID, three times daily.

# Cytisinicline for smoking cessation: a randomized trial enrolled hard-to-treat patients[1]

POOLED ORCA-2 AND ORCA-3 SAFETY SET (N=1,594)[2]

**52**
mean age, enrolled to 84; 1 in 7 aged 65 or older

**36**
mean years of smoking

**42%**
had tried varenicline and were still smoking

**~20%**
had tried bupropion and were still smoking

**4**
median prior quit attempts before ORCA-2 or ORCA-3

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) |

PUBLISHED

JAMA

## Table 1 from ORCA-2[1]

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

[b] Fagerstrom Test for Nicotine Dependence 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 is a 14-item self-administered scale, with a range of scores 0 to 42. Higher scores indicate more symptoms of anxiety and depression.

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1. 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. 2. Data on file, Achieve Life Sciences: pooled ORCA-2 and ORCA-3 safety set (participants who took at least one dose).

# Enrollment criteria and baseline characteristics: ORCA versus the varenicline and bupropion Phase 3 trials

| | Cytisinicline Phase 3<br>ORCA-2; ORCA-3[1-3] | Varenicline (Chantix®) Phase 3<br>Gonzales 2006; Jorenby 2006[4,5] | Bupropion SR (Zyban®) Phase 3<br>Hurt 1997; Jorenby 1999[6,7] |
|---|---|---|---|
| Age | Mean 52; no upper limit<br>enrolled ages 18 to 84 | Mean 43; capped at 75<br>ages 18 to 75 | Mean 43<br>ages 18 and older; cap not stated |
| Prior varenicline or bupropion | Enrolled<br>before ORCA, 42% had tried varenicline and 20% bupropion, and were still smoking | Excluded<br>any prior bupropion or varenicline | Excluded<br>prior bupropion; varenicline not yet approved |
| Years smoking, mean | 36 | 25 | 26<br>only reported in Jorenby 1999 |
| Biochemically verified smoking status at entry | Required<br>exhaled CO 10 ppm or more | Self-report CPD only<br>no CO threshold for entry | Self-report CPD only<br>no CO threshold for entry |
| Depression on treatment | Enrolled<br>medication continued; current moderate-to-severe symptoms (HADS ≥ 11) excluded | Excluded<br>treatment for major depression in the previous 12 months | Excluded<br>current depression or psychoactive drug use |
| Other medications | All continued<br>Only quit drugs such as varenicline or bupropion barred | Restricted<br>quit drugs (NRT, bupropion, clonidine, nortriptyline) and diabetes drugs barred; MAOIs also in Jorenby 2006 | Restricted<br>psychoactive drugs and NRT barred in both trials |
| Heart disease | Enrolled<br>only acute events in the prior 3 months excluded | Excluded if within 6 months<br>significant cardiovascular disease | Restricted<br>serious or unstable heart disease excluded |
| Diabetes | Enrolled | Excluded<br>if on insulin or oral agents | Restricted<br>serious or unstable endocrine disease excluded |
| Cancer history | Enrolled | Excluded<br>history of cancer (Gonzales 2006 allowed skin carcinoma) | Restricted<br>generally good health required, brain tumor history specifically excluded |
| COPD | Enrolled<br>any severity | Excluded<br>severe COPD | Restricted<br>serious or unstable lung disease excluded |
| Alcohol abuse or dependence | Not excluded | Excluded<br>in the prior 12 months | Excluded<br>in the prior 12 months |

Varenicline and bupropion trial means weighted across all randomized arms. ORCA excluded myocardial infarction, unstable angina, stroke, or heart failure hospitalization in the prior 3 months, and uncontrolled hypertension (≥160/100 mm Hg). Varenicline trials excluded clinically significant cardiovascular disease or serious or unstable disease in the prior 6 months; Jorenby 2006 also excluded baseline blood pressure >150/95 mm Hg. CPD, cigarettes per day.

1. Rigotti NA, et al. JAMA. 2023;330:152-160. 2. Rigotti NA, et al. JAMA Intern Med. 2025;185:648-655. 3. Data on file: ORCA-2 and ORCA-3 Clinical Study Reports; Integrated Summary of Safety (Phase 3 Pool). 4. Gonzales D, et al. JAMA. 2006;296:47-55. 5. Jorenby DE, et al. JAMA. 2006;296:56-63. 6. Hurt RD, et al. N Engl J Med. 1997;337:1195-1202. 7. Jorenby DE, et al. N Engl J Med. 1999;340:685-691.

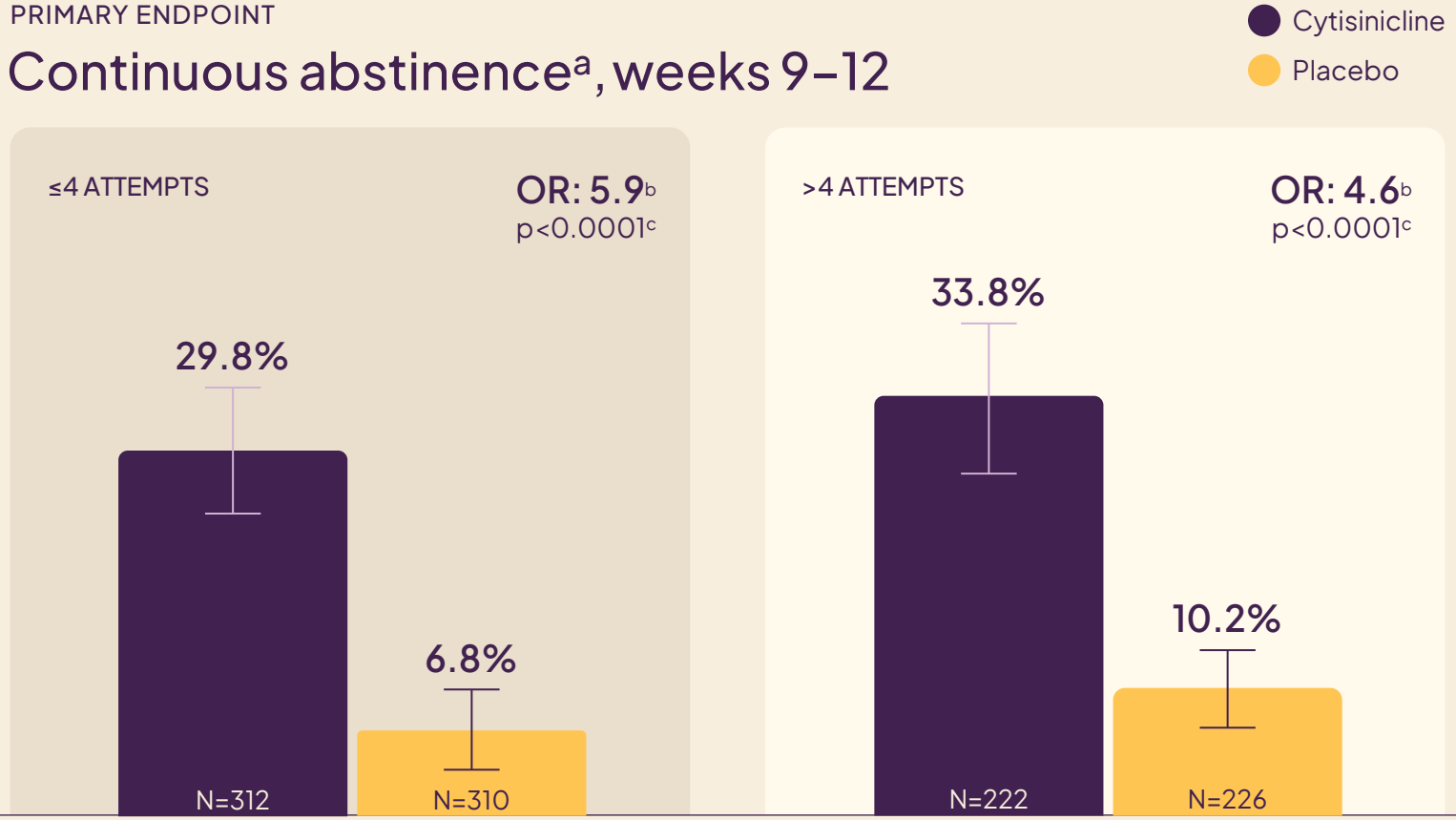
PRESENTED

SOCIETY FOR RESEARCH ON NICOTINE & TOBACCO

# Cytisinicline showed higher odds of quitting versus placebo regardless of number of prior quit attempts[1]

PRIMARY ENDPOINT

## Continuous abstinence[a], weeks 9–12




NEARLY

**5–6-fold**

higher odds of quitting vs placebo regardless of number of prior quit attempts

**Pooled data from ORCA-2 and ORCA-3**

1. Data presented at the Society for Research on Nicotine & Tobacco (SRNT) Annual Meeting, March 2026. https://achievelifesciences.com/products/resources/
Post hoc analysis of pooled ORCA-2 and ORCA-3 data. a. Continuous CO-verified smoking abstinence, weeks 9–12; b. vs placebo; c. P-value for difference in proportion, via Cochran-Mantel-Haenszel test. Error bars represent 95% CI. CO, carbon monoxide; OR, odds ratio.

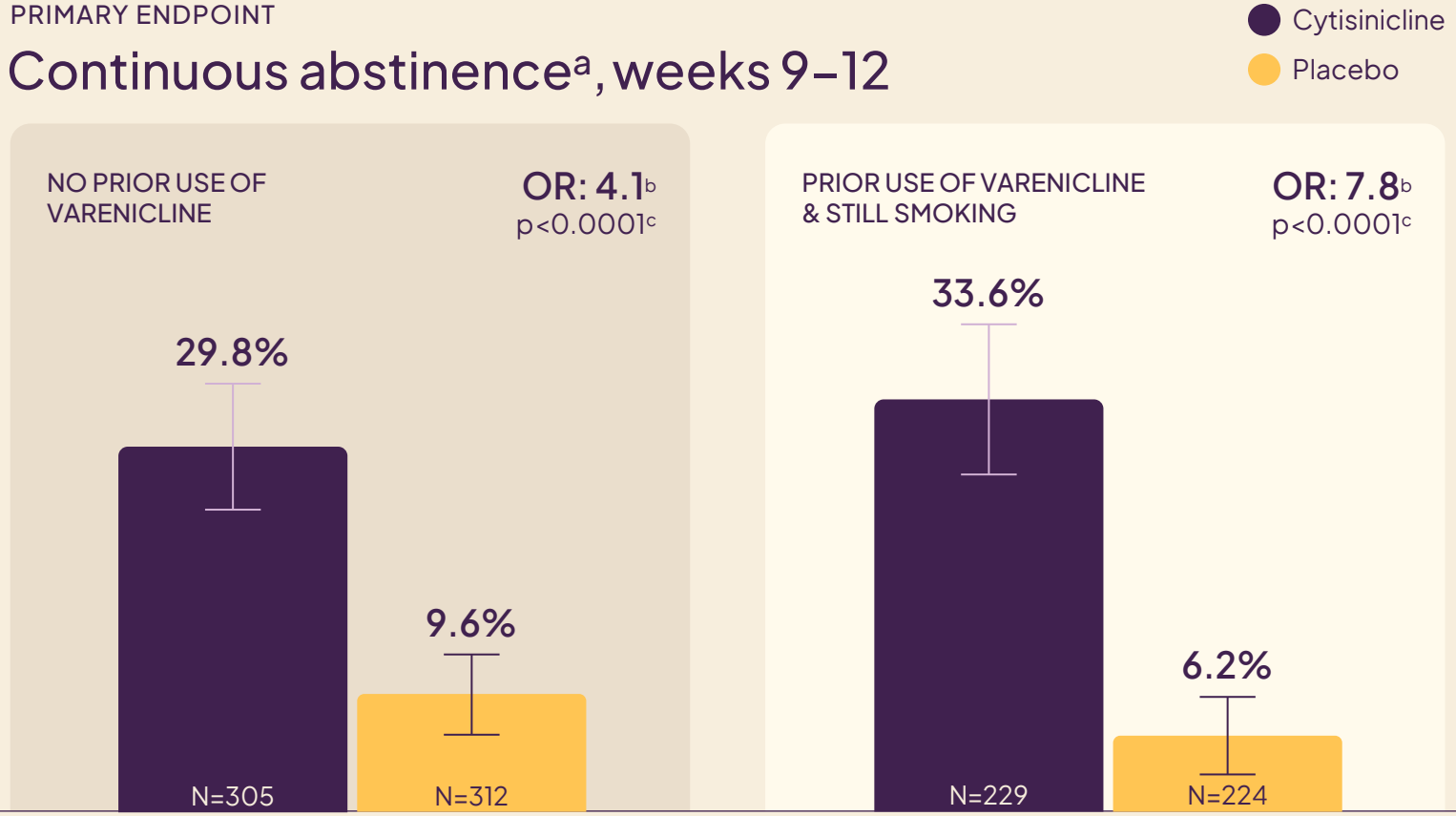
PRESENTED

SOCIETY FOR RESEARCH ON NICOTINE & TOBACCO

# Cytisinicline showed higher odds of quitting versus placebo regardless of prior varenicline use[1]

PRIMARY ENDPOINT

## Continuous abstinence[a], weeks 9–12




APPROXIMATELY

**8-fold**

higher odds of quitting vs placebo with prior varenicline exposure and still smoking

**Pooled data from ORCA-2 and ORCA-3**

1. Data presented at the Society for Research on Nicotine & Tobacco (SRNT) Annual Meeting, March 2026. https://achievelifesciences.com/products/resources/
Post hoc analysis of pooled ORCA-2 and ORCA-3 data. a. Continuous CO-verified smoking abstinence, weeks 9–12; b. vs placebo; c. P-value for difference in proportion, via Cochran-Mantel-Haenszel test. Error bars represent 95% CI. CO, carbon monoxide; OR, odds ratio.

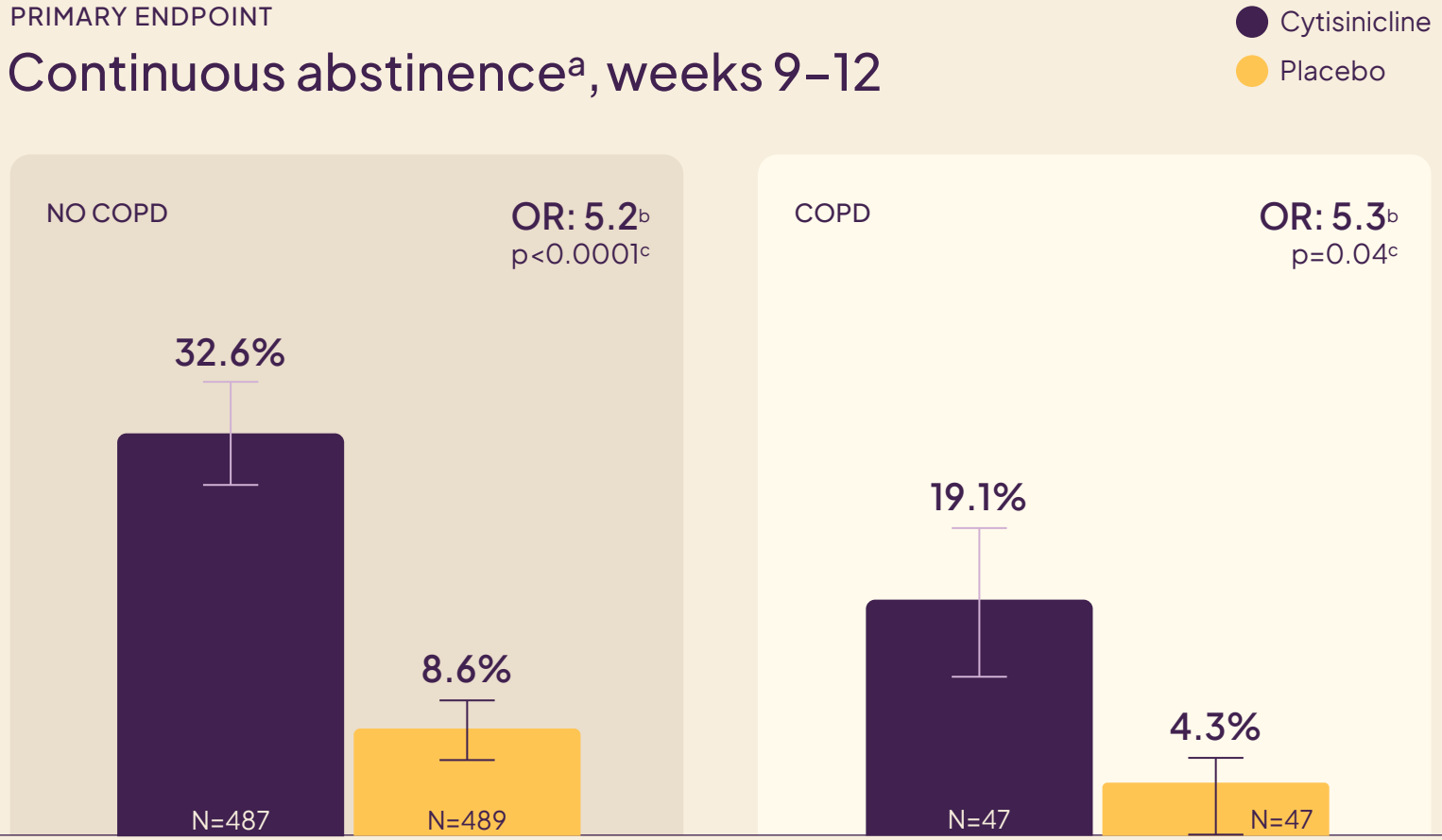
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Thorax
AN INTERNATIONAL JOURNAL OF RESPIRATORY MEDICINE

# Potential efficacy in hard-to-treat populations, such as people with COPD who smoke[1]

PRIMARY ENDPOINT

## Continuous abstinence[a], weeks 9–12




OVER

**5-fold**

higher odds of quitting vs placebo whether or not patients had COPD, a high unmet-need population

**Pooled data from ORCA-2 and ORCA-3**

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, weeks 9–12; b. vs placebo; c. P-value for difference in proportion, via Cochran-Mantel-Haenszel test. Error bars represent 95% CI. CO, carbon monoxide; OR, odds ratio.

PUBLISHED

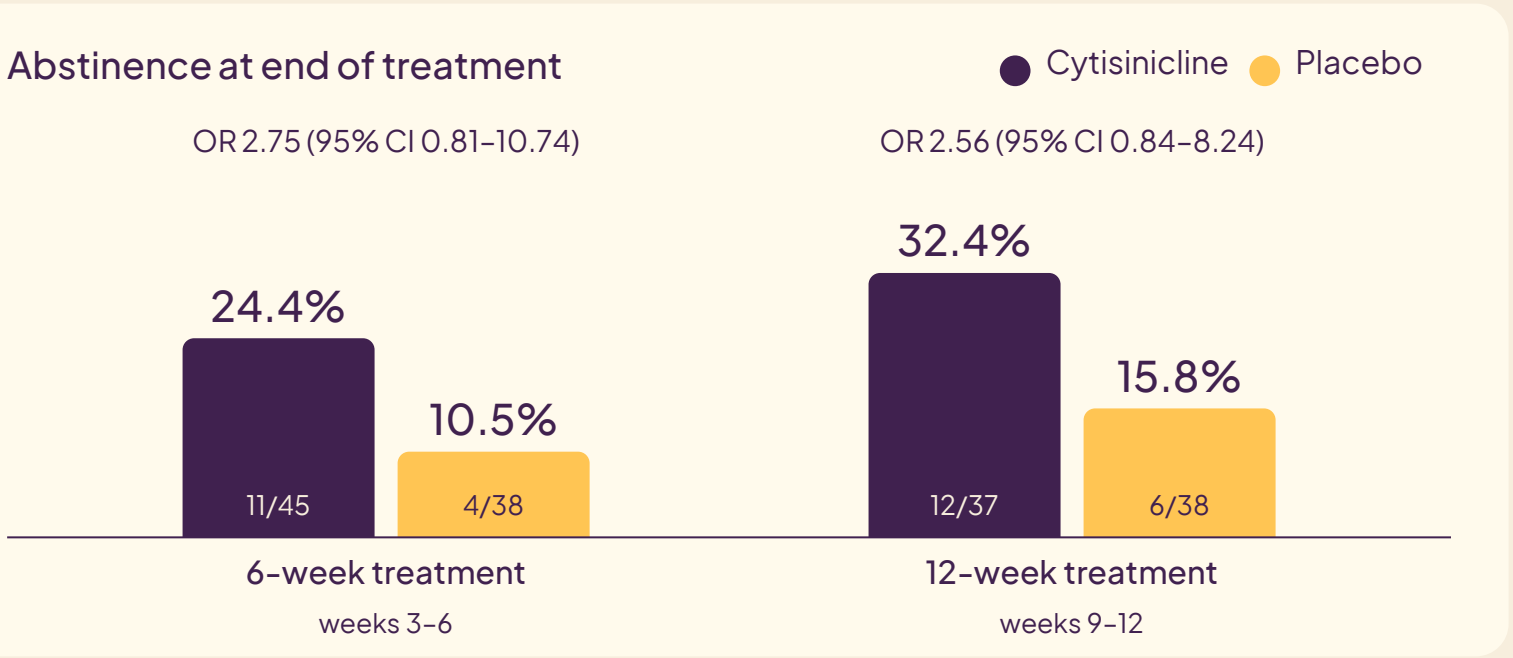
ASCO® AMERICAN SOCIETY OF CLINICAL ONCOLOGY

ASCO 2026 Annual Meeting

Abstract #e22676, publication only

# Cytisinicline in cancer survivors: well tolerated, numerically higher quit rates[1]

Post hoc analysis of ORCA-2 and ORCA-3 participants with a history of cancer




## Participants

120 of 1,602 randomized participants (ITT)

Mean age 60.6; mean smoking duration 44.4 years

Most common cancers: basal cell (31), breast (21), squamous cell (19)

## Safety

No serious treatment-related adverse events

Under 3% discontinued due to adverse events

Most common TEAEs: insomnia, abnormal dreams

"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."

*ASCO 2026 abstract, Conclusions*

1. J Clin Oncol. 2026;44(16 suppl):e22676 (ASCO Annual Meeting 2026, publication only). Post hoc, exploratory analysis.

# Quitting smoking after a cancer diagnosis, even at an advanced stage, is associated with reduced mortality[1]

**1–2 years** longer survival when people with cancer quit smoking[2,3]

**~2x** risk of death with smoking during radiation therapy in certain cancers[4,5]

ORIGINAL RESEARCH

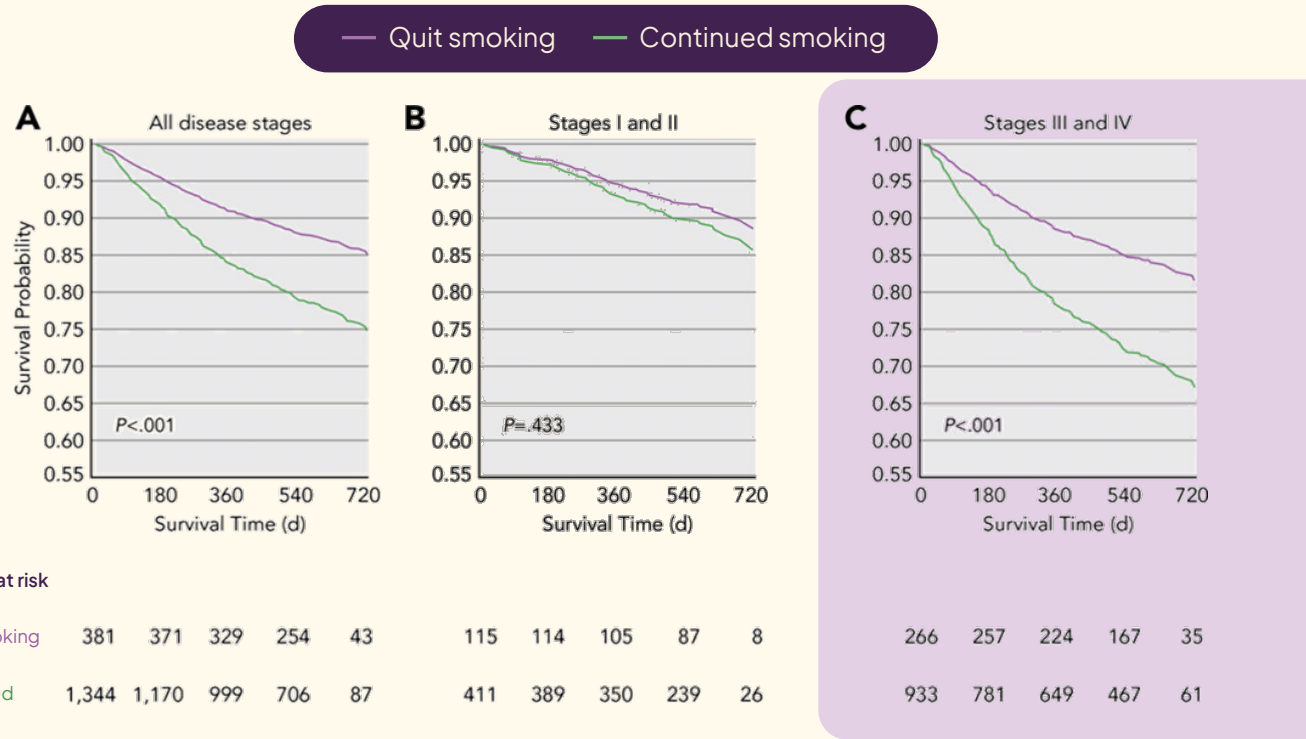
## Smoking Cessation and Mortality Risk in Cancer Survivorship: Real-World Data From a National Cancer Institute–Designated Cancer Center

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*

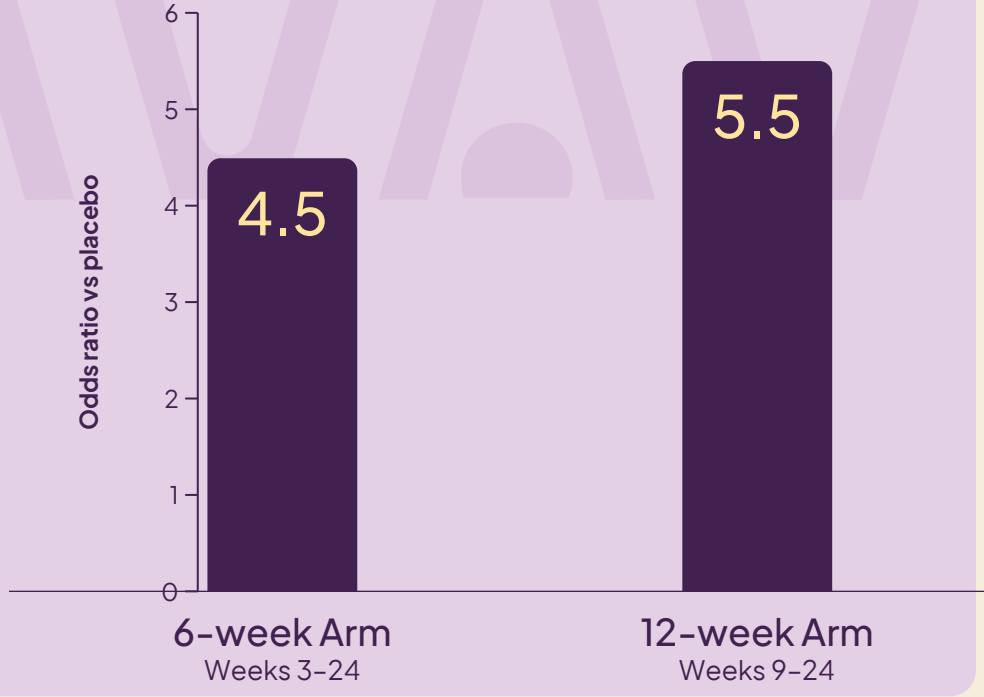



1. Tohmasi S, et al. J Natl Compr Canc Netw. 2025;23(10):e257059. doi:10.6004/jnccn.2025.7059
2. Cinciripini PM, et al. JAMA Oncol. 2024;10(12):1689-1696. doi:10.1001/jamaoncol.2024.4890
3. Sheikh M, et al. Ann Intern Med. 2021;174(9):1232-1239. doi:10.7326/M21-0252
4. Smith J, et al. Radiother Oncol. 2019;135:51-57. doi:10.1016/j.radonc.2019.02.021
5. Steinberger E, et al. BJU Int. 2015;116(4):596-603. doi:10.1111/bju.12969

# Continuous quitting at the end of treatment and beyond, through week 24

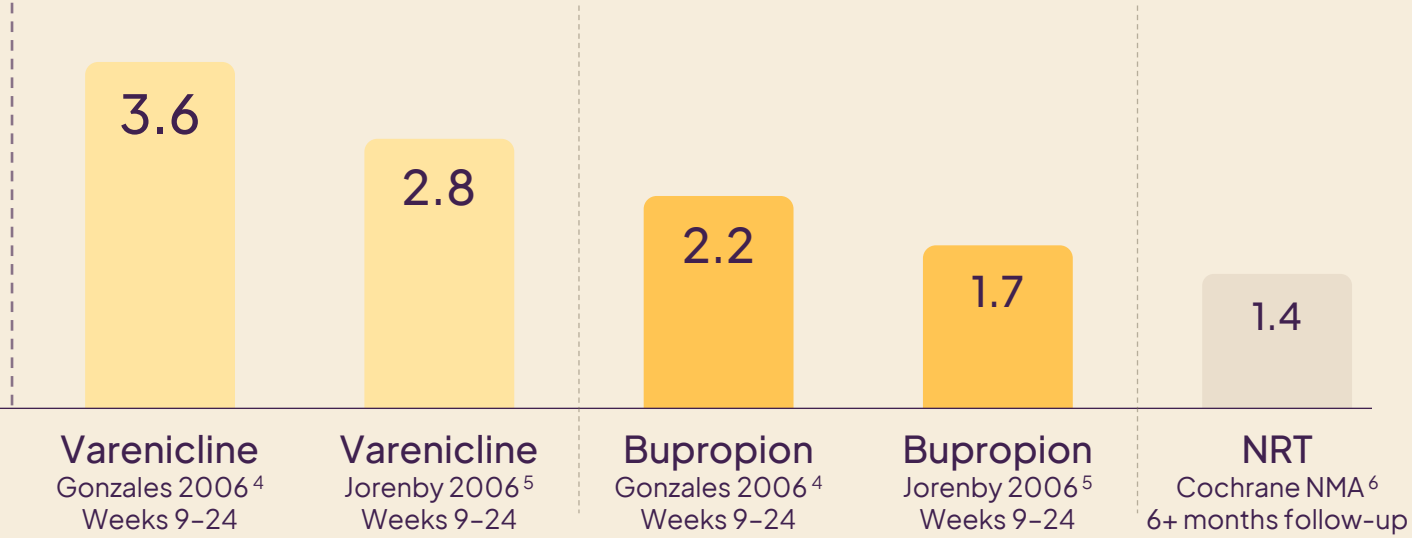
Odds of sustained quitting over placebo

## Cytisinicline Pooled Phase 3 Data [1-3]




## Currently Approved Treatments: Phase 3 Trials [4-6]

No head-to-head trials of cytisinicline versus approved therapies
Varenicline and bupropion odds ratios are from the same three-arm Phase 3 trials




Cytisinicline odds ratios are derived from the pooled ORCA-2 and ORCA-3 Phase 3 trials, measured as continuous abstinence during weeks 3–24 and 9–24 versus placebo. Varenicline odds ratios are derived from the Gonzales 2006 and Jorenby 2006 Phase 3 trials, measured as continuous abstinence during weeks 9–24 versus placebo. Odds ratios for bupropion SR vs placebo (weeks 9–24) calculated from published rates in Gonzales et al. 2006 and Jorenby et al. 2006; not directly reported in source publications. NRT odds ratios are derived from Cochrane's network meta-analysis, which pooled studies with follow-up ranging from 6 months to 5 years (predominantly 6 to 12 months).


1. Data on file – Achieve Life Sciences integrated Phase 3 pooled data.
2. Rigotti NA, Benowitz NL, Prochaska J, Leischow S, Nides M, Blumenstein B, Clarke A, Cain D, Jacobs C. Cytisinicline for Smoking Cessation: A Randomized Clinical Trial. JAMA. 2023 Jul 11;330(2):152-160.
3. Rigotti NA, Benowitz NL, Prochaska JJ, Rubinstein M, Clarke A, Blumenstein B, Cain DF, Jacobs C. Cytisinicline for Smoking Cessation: The ORCA Phase 3 Replication Randomized Clinical Trial. JAMA Intern Med. 2025 Jun 1;185(6):648-655.
4. Gonzales D, Rennard SI, Nides M, Oncken C, Azoulay S, Billing CB, Watsky EJ, Gong J, Williams KE, Reeves KR, Varenicline Phase 3 Study Group. Varenicline, an α4β2 nicotinic acetylcholine receptor partial agonist, vs sustained-release bupropion and placebo for smoking cessation: a randomized controlled trial. JAMA. 2006 Jul 5;296(1):47-55.
5. Jorenby DE, Hays JT, Rigotti NA, Azoulay S, Watsky EJ, Williams KE, Billing CB, Gong J, Reeves KR, Varenicline Phase 3 Study Group. Efficacy of varenicline, an α4β2 nicotinic acetylcholine receptor partial agonist, vs placebo or sustained-release bupropion for smoking cessation: a randomized controlled trial. JAMA. 2006 Jul 5;296(1):56-63.
6. Lindson N, Theodoulou A, Ordóñez-Mena JM, Fanshawe TR, Sutton AJ, Livingstone-Banks J, Hajizadeh A, Zhu S, Aveyard P, Freeman SC, Agrawal S, Hartmann-Boyce J. Pharmacological and electronic cigarette interventions for smoking cessation in adults: component network meta-analyses. Cochrane Database of Systematic Reviews. 2023;2023(9):CD015226.

# Chemistry, not character

# Cytisinicline was generally well tolerated: under 4% discontinued due to TEAEs[1]

Data from the ORCA-2 and ORCA-3 Phase 3 trials (safety set, N=1,594); cytisinicline 6- and 12-week arms pooled; values are n (%)

| | | Placebo (N=532), n (%) | Cytisinicline, 6- and 12-week pooled (N=1,062), n (%) |
|---|---|---|---|
| | At least 1 TEAE | 330 (62.0) | 694 (65.3) |
| ≥5% TEAEs[a] | Insomnia | 33 (6.2) | 109 (10.3) |
| | Abnormal dreams | 23 (4.3) | 87 (8.2) |
| | Nausea | 39 (7.3) | 74 (7.0) |
| | Headache | 38 (7.1) | 81 (7.6) |
| | At least 1 treatment-related TEAE | 150 (28.2) | 404 (38.0) |
| | At least 1 serious TEAE | 11 (2.1) | 34 (3.2) |
| | At least 1 treatment-related serious TEAE | 0 | 0 |
| Discontinuation Rates | At least 1 TEAE leading to discontinuation | 10 (1.9) | 38 (3.6) |
| | At least 1 treatment-related TEAE leading to discontinuation | 4 (0.8) | 26 (2.4) |

1. Data on file, Achieve Life Sciences: Integrated Summary of Safety, ORCA-2 and ORCA-3 Phase 3 pool (safety set). a. TEAE terms occurring in ≥5% of either cytisinicline arm, excluding COVID-19.

# Tolerability, label warnings, interactions, and duration of current FDA-approved options

| | Varenicline<br>Chantix® | Bupropion SR<br>Zyban® | OTC nicotine replacement<br>Patch, gum, lozenge |
|---|---|---|---|
| Tolerability | **Nausea in up to 30%, and 40% in a 52-week study[1,2]**<br>4.4x the odds of nausea vs placebo;[3] 40.2% nausea and approximately half of participants completed the 52-week study (53.8% varenicline arm);[2] 60.5% to 65% of participants completed the 12-week Phase 3 trials[4,5] | **Insomnia in up to 40%[6]**<br>8% discontinued due to adverse reactions[6] | **Varies by product[7-9]**<br>Skin reactions (patch);[7] mouth, teeth or jaw problems (gum);[8] mouth problems or sore throat (lozenge);[9] hiccups, heartburn and nausea if gum or lozenge are used incorrectly[8,9] |
| Label warnings | **No boxed warning (removed 2016)[1]**<br>9 warnings and precautions: neuropsychiatric events, seizures, interaction with alcohol, somnambulism, nausea, and others[1] | **Boxed warning[6]**<br>For suicidal thoughts and behaviors in children, adolescents, and young adults taking antidepressants; 8 warnings and precautions; contraindicated in seizure disorders and in current or prior anorexia nervosa or bulimia[6] | **No boxed warning[7-9]**<br>Sold over the counter[7-9] |
| Drug interactions | **Few[1]**<br>No clinically meaningful pharmacokinetic interactions[1] | **Multiple[6]**<br>Inhibits CYP2D6, can raise levels of antidepressants, antipsychotics, beta-blockers and Type 1C antiarrhythmics[6] | **Few[7-9]** |
| Duration | **12 to 24 weeks[1]**<br>1-week titration; second 12-week course recommended for those who quit[1] | **7 to 12 weeks or longer[6]**<br>Stopping recommended if not working; ongoing treatment considered for those who quit[6] | **8 to 12 weeks[7-9]**<br>Potentially longer (consult healthcare provider); gum and lozenge are used many times a day[7-9] |

1. Chantix (varenicline) tablets. Prescribing information. Pfizer Inc; revised 6/2025. Section 5 warnings and precautions: neuropsychiatric adverse events including suicidality; seizures; interaction with alcohol; accidental injury; cardiovascular events; somnambulism; angioedema and hypersensitivity reactions; serious skin reactions; nausea. Boxed warning removed 12/2016 (prescribing information revised 12/2016). 2. Williams KE, et al. Curr Med Res Opin. 2007;23(4):793-801. 3. Drovandi AD, et al. Curr Drug Saf. 2016;11(1):78-85. 4. Gonzales D, et al. JAMA. 2006;296(1):47-55. 5. Jorenby DE, et al. JAMA. 2006;296(1):56-63. 6. Bupropion hydrochloride extended-release tablets (SR). Prescribing information. Dr. Reddy's Laboratories Inc; revised 10/2025. Section 5 warnings and precautions: suicidal thoughts and behaviors in children, adolescents, and young adults; neuropsychiatric adverse events and suicide risk in smoking cessation treatment; seizure; hypertension; activation of mania/hypomania; psychosis and other neuropsychiatric reactions; angle-closure glaucoma; hypersensitivity reactions. 7. NicoDerm CQ (nicotine transdermal system). Drug Facts label. Haleon US Holdings LLC; DailyMed updated July 2025. 8. Nicorette (nicotine polacrilex gum). Drug Facts label. Haleon US Holdings LLC; DailyMed updated August 2024. 9. Nicorette (nicotine polacrilex lozenge). Drug Facts label. Haleon US Holdings LLC; DailyMed updated April 2025. References 7 to 9 are Drug Facts labels for the reference brand OTC NRT products; generic equivalents carry equivalent labeling.

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# Minimal 5-HT3 binding may support a favorable tolerability profile[1]

Serotonin (5-hydroxytryptamine) 5-HT3 is a receptor commonly associated with nausea and vomiting[2]

**"Cytisinicline selectively targets the α4β2 nicotinic receptor with minimal interaction with the 5-HT3 receptor."[1]**

*Rubinstein and Jacobs 2026, Abstract: Conclusions*

Receptor Binding

| BINDING ASSAY[a] | % DISPLACEMENT |
|---|---|
| Nicotinic acetylcholine α4β2<br>On-target receptor | 99 |
| Serotonin (5-HT3)<br>Off-target: linked to nausea | −8 |

## Receptor binding

### NICOTINE

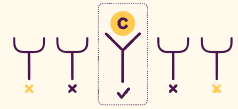
**"Nicotine is the drug in tobacco that causes addiction."[3]**

"Nicotine … is an agonist at the nicotinic acetylcholine receptors (nAChRs) expressed both in the peripheral nervous system and the CNS."[3]




### CYTISINICLINE

**Cytisinicline binds to nicotinic receptors.[1]**




"Cytisinicline (10 μM) displaced 99% of the radiolabeled test ligand specific for the α4β2 nicotinic receptor, while at the same concentration, cytisinicline demonstrated no significant displacement of the radiolabeled test ligand for the 5-HT3 receptor (−8%), indicating a lack of measurable binding under the assay conditions."[1]

*Rubinstein and Jacobs 2026, Abstract: Results*

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

1. Rubinstein ML, Jacobs C. Receptor selectivity of cytisinicline: minimal 5-HT3 binding may explain lower incidence of nausea in smoking cessation therapy. Nicotine Tob Res. 2026; published online March 26, 2026. doi:10.1093/ntr/ntag039. Quotations are verbatim from the published article. 2. Hesketh PJ. Chemotherapy-induced nausea and vomiting. N Engl J Med. 2008;358(23):2482-2494. 3. U.S. Department of Health and Human Services. How Tobacco Smoke Causes Disease: The Biology and Behavioral Basis for Smoking-Attributable Disease. A Report of the Surgeon General. Atlanta, GA: CDC; 2010. Chapter 4, Nicotine Addiction: Past and Present.

# Matching-adjusted indirect comparison: Cytisinicline vs Varenicline

MAIC-estimated higher odds of quitting vs varenicline at weeks 9–24; estimated lower odds of nausea vs varenicline

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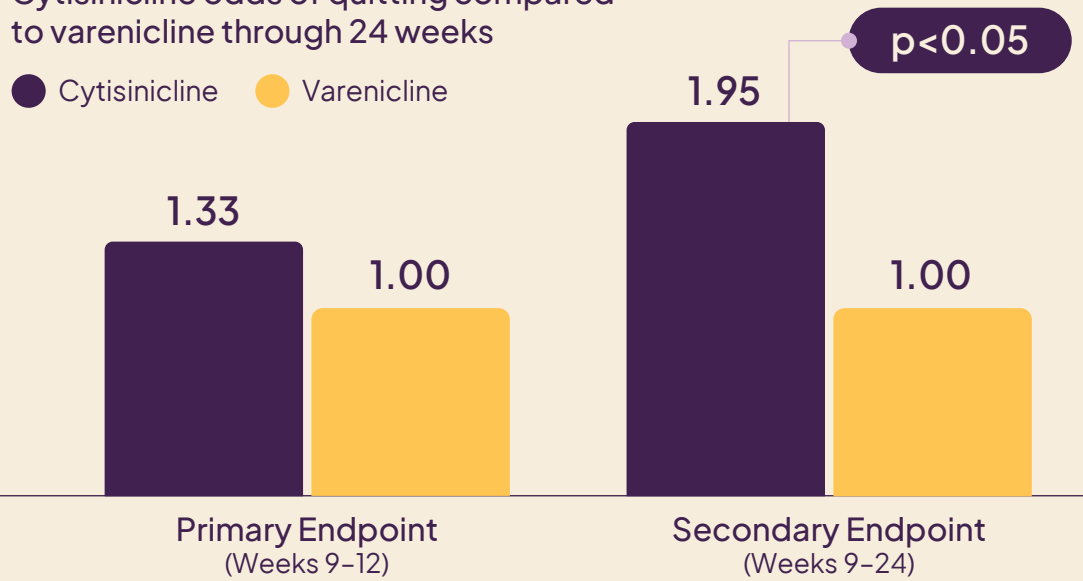
Journal of Health Economics and Outcomes Research

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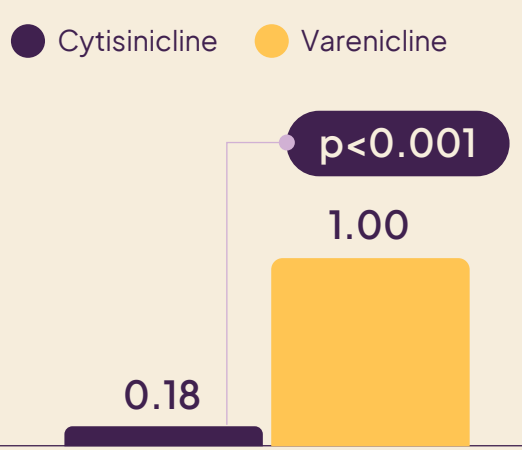
ATS 2026

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.[1]

Cytisinicline odds of quitting compared to varenicline through 24 weeks




Cytisinicline odds of nausea compared to varenicline




The estimated 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, Rowe D, Perdok R, Jacobs C. Comparative Effectiveness of Cytisinicline and Varenicline for Smoking Cessation: A Matching-Adjusted Indirect Comparison (MAIC). JHEOR. 2026;13(1):182-188. doi:10.36469/001c.160017. 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

# Vaping program

# FDA granted cytisinicline Breakthrough Therapy designation and a National Priority Voucher for vaping cessation

2024

## Breakthrough Therapy designation[1]

Reserved for therapies showing potential for substantial improvement over existing options, and it opens expedited development with direct FDA guidance.

2025

## Commissioner's National Priority Voucher[2]

A new program accelerating review of treatments that address major public-health priorities. Cytisinicline was among the first ever selected.

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

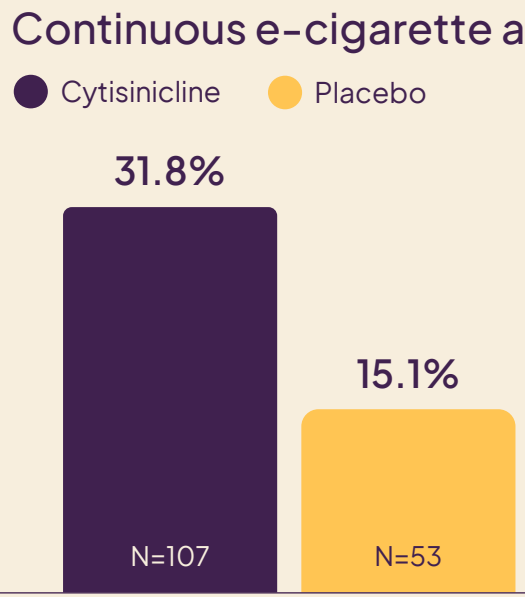
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JAMA Internal Medicine

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




### Primary Outcome
End of treatment (Weeks 9–12)

**OR 2.64**

95% CI 1.06–7.10
p=0.035

1. 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.

# 52 weeks of continuous therapy

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ATS 2026

# 52-week continuous therapy was generally well tolerated with no new safety signals[1]

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

Nancy A Rigotti,[1] Renee Perdok,[2] Matthew Linley-Adams,[2]* Mark L Rubinstein[2]

[1]Tobacco Research and Treatment Center, Department of Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA; [2]Achieve Life Sciences, Seattle, WA, USA.
*Presenting author

Digital poster available via QR code

Poster: #325

### Introduction

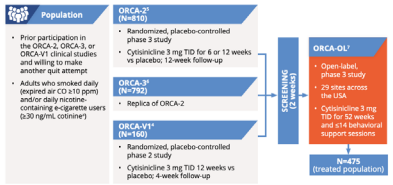
- Approximately 25 million adults in the USA smoke,[1] and no new FDA-approved smoking cessation therapies have been introduced since 2006[2]
- Approximately 18 million adults in the USA use electronic (e)-cigarettes,[3] with no FDA-approved treatments indicated specifically as an aid to nicotine e-cigarette 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

## 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

1. Rigotti NA, et al. ORCA-OL 52-week safety data. Poster #325, American Thoracic Society (ATS) 2026 International Conference, May 15–20, 2026, Orlando, FL (NCT06435221). Cytisinicline is investigational and not approved by the FDA.

# ORCA-OL: quit rates rose and held to week 52

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**CHEST 2026 Annual Meeting**
*Late-breaking abstract, rapid oral presentation*

Open-label cytisinicline for 52 weeks (N=475): every participant was still smoking and/or vaping after a prior ORCA trial[1]

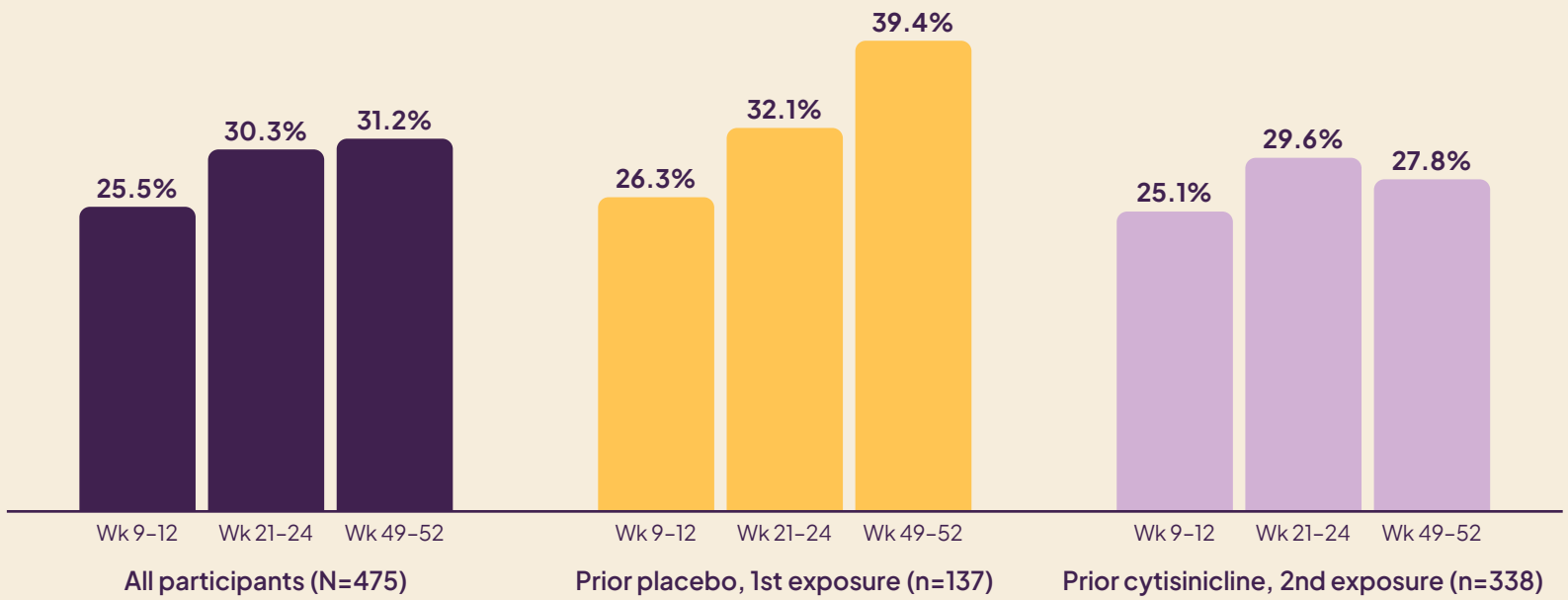
**338**
71.2% received cytisinicline (6- or 12-week arm) and were still smoking and/or vaping: a second exposure

**137**
28.8% received placebo and were still smoking and/or vaping: a first exposure to cytisinicline

**The typical participant who smoked in ORCA-OL had an estimated 5 prior quit attempts[a]**

**4-WEEK CONTINUOUS BIOMARKER VERIFIED ABSTINENCE THROUGH 52 WEEKS**

Participants abstinent (%)




**First exposure:** abstinence kept rising with continued treatment, 26% to 39% at one year.
**Second exposure:** abstinence was achieved and held near 30% across the year.

Prior treatment as randomized in the first ORCA study (cytisinicline = 6- or 12-week arms). Enrollment required current smoking or vaping. 4-week continuous abstinence, biochemically verified (CO <10 ppm or plasma cotinine <10 ng/mL); participants with missing data counted as not abstinent. Descriptive; single-arm, no comparator. Prior-trial quit rates are end-of-treatment (weeks 9–12) rates from ORCA-2/3 and ORCA-V1. a. Estimate: median 4 previous quit attempts at ORCA-2/3 screening (ISS) plus the ORCA trial; ORCA-OL cohort figure pending.

1. Rubinstein ML, Prochaska J, Benowitz N, Hatsukami D, Rigotti N, Linley-Adams M. Efficacy of 52-week cytisinicline treatment for cigarette smoking and e-cigarette cessation: the open-label ORCA-OL trial. Late-breaking abstract and rapid oral presentation, CHEST 2026 Annual Meeting (NCT06435221). Cytisinicline is investigational and not approved by the FDA.

# Multiple value drivers designed to de-risk potential approval

## Large, underserved market

~38M U.S. adults who smoke, vape, or both, with no new medicine to help people quit smoking in two decades and none ever approved to help people quit vaping.[1,2]

## Demonstrated efficacy

Over 5-fold higher odds of quitting vs placebo in pooled Phase 3 trials; efficacy shown in hard-to-treat subgroups (COPD and many prior quit attempts).[3-6]

## Favorable tolerability profile

Minimal 5-HT3 receptor binding is potentially associated with lower nausea rates than other therapies[7]

## Defined regulatory path

NDA resubmission planned for Q4 2026, supported by 1,500+ participants exposed to cytisinicline; safety data in 400+ participants at 6+ months and 200+ at 1 year.[8,9]

## Resourced for launch

Up to $354M in financing positions AchieveRx to execute from day one.[10]

1. Agaku I. Tobacco Product Use among U.S. Adults, 2023-2024. NEJM Evidence. 2026. doi:10.1056/EVIDpha2500339. ~38M derived as 25.2M who smoke + 17.8M who vape (2024) minus ~4.5M who do both (2023; Arrazola RA, et al. MMWR Morb Mortal Wkly Rep. 2025;74:118-121). 2. U.S. Public Health Service, Office of the Surgeon General. Smoking Cessation: A Report of the Surgeon General. HHS; 2020. 3. Rigotti NA, et al. JAMA. 2023;330(2):152-160. 4. Rigotti NA, et al. JAMA Intern Med. 2025;185(6):648-655. 5. Prochaska JJ, et al. Thorax. 2025;81(2):164 (COPD). 6. Data presented at the SRNT Annual Meeting, March 2026 (prior quit attempts). 7. Rubinstein ML, Jacobs C. Nicotine Tob Res. 2026. doi:10.1093/ntr/ntag039. 8. Achieve Life Sciences. Third quarter 2026 financial results and corporate update. Press release, November 2026. 9. Data on file: Integrated Summary of Safety (Phase 3 Pool); Rubinstein ML, et al. CHEST 2026 late-breaking abstract (ORCA-OL, NCT06435221). 10. Achieve Life Sciences. Press release, June 2026 (financing). Cytisinicline is investigational and not approved by the FDA.




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