Cytisinicline for Smoking Cessation: Effectiveness and Value

Final Report

FEBRUARY 12, 2026

Prepared for

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Jeffrey A. Tice served as the lead author for the report. Dmitriy Nikitin led the systematic review and authorship of the comparative clinical effectiveness section of this report with assistance from Sol Sanchez. Josh Carlson, Kangho Suh and Hui-Hsuan Chan developed the cost-effectiveness model and authored the corresponding sections of the report. Marina Richardson and Marie Phillips conducted analyses for the budget impact model. David Rind provided methodologic guidance on the clinical and economic evaluations. We would also like to thank Temiwunmi Shobanke, Sophia Cassim, Chloe Fandetti, Grace Ham, and Anna Geiger for their contributions to this report.

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For drug topics, in addition to receiving recommendations from the public, ICER scans publicly available information and also benefits from a collaboration with IPD Analytics, an independent organization that performs analyses of the emerging drug pipeline for a diverse group of industry stakeholders, including payers, pharmaceutical manufacturers, providers, and wholesalers. IPD provides a tailored report on the drug pipeline on a courtesy basis to ICER but does not prioritize topics for specific ICER assessments.

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Midwest CEPAC directly engages clinicians, patients, and payers during public meetings to discuss implications of the evidence for clinical decision-making and coverage policies. Application of evidence takes shape through new medical policies, benefit designs, and patient and clinician tools to improve clinical care and patient outcomes.

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In the development of this report, ICER's researchers consulted with clinical experts, patients, manufacturers, and other stakeholders. The following individuals served as external reviewers of the draft evidence report:

Expert Reviewers

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None of the external reviewers or other experts we spoke to are responsible for the final contents of this report, nor should it be assumed that they support any part of it. Furthermore, it is possible that external reviewers may not have had the opportunity to review all portions of the draft report. The report should be viewed as attributable solely to the ICER team and its affiliated researchers.

To protect patient confidentiality, ICER does not routinely name individual patients or care partners who provided us with input and feedback.

For a list of stakeholders from who we requested input from, or who have submitted public comments so far, please visit: https://icer.org/wp-content/uploads/2025/09/ICER_Smoking-Cessation_Stakeholder-List_For-Publication_090525.pdf

Conflict of Interest Disclosures for the Report

Table 1. ICER Staff and External Collaborators Conflict of Interest Disclosures

ICER Staff and External Collaborators	Conflict of Interest
Josh Carlson, PhD, MPH	No conflicts to disclose.
Hui-Hsuan Chan, MHS	No conflicts to disclose.
Anna Geiger, BS	No conflicts to disclose.
Kelsey Gosselin, MA	No conflicts to disclose.
Grace Ham, MSc	No conflicts to disclose.
Max Lee, PharmD	No conflicts to disclose.
Dmitriy Nikitin, MSPH	No conflicts to disclose.
Marie Phillips, BA	No conflicts to disclose.
Marina Richardson, PhD, MSc	No conflicts to disclose.
David M. Rind, MD, MSc	No conflicts to disclose.
Sol Sanchez, BA	No conflicts to disclose.
Temiwunmi Shobanke, MS	No conflicts to disclose.
Kangho Suh, PharmD, PhD	No conflicts to disclose.
Jeffrey A. Tice, MD	No conflicts to disclose.

Table 2. Expert Reviewers of the Draft Evidence Report Conflict of Interest Disclosures

Expert Reviewer	Conflict of Interest
Nancy A. Rigotti, MD Professor of Medicine, Harvard Medical School; Director, Tobacco Research & Treatment Center, Massachusetts General Hospital	Dr. Rigotti has received funding for helping to design, conduct, and reporting results of research trials of cytisinicline for smoking cessation and electronic cigarette cessation from Achieve Life Sciences with funds paid to Massachusetts General Hospital. She was the principal investigator for ORCA-2 and ORCA-V1. Dr. Rigotti also received consulting fees from Achieve Life Sciences through the end of 2022, but not since that time.
Kednapa Thavorn, PhD Senior Scientist and Scientific Lead of Health Economics, Ottawa Hospital Research Institute	Dr. Thavorn has no conflicts to disclose.
Natalie Walker, PhD Professor and Director of the Flinders Clinical Trials Platform, Flinders Health and Medical Research Institute (FHMRI), College of Medicine and Public Health, Flinders University, South Australia	Dr. Walker led an investigator-initiated smoking cessation trial in New Zealand, funded by the New Zealand Health Research Council. One of the trial treatments was cytisine (Tabex®), which was provided at no cost to the trial by Achieve Life Sciences, via Sopharma (Bulgaria). These companies were not involved in the design, conduct or analysis of the trial.
Linda Walsh Chief Mission Officer, COPD Foundation	Linda Walsh has no conflicts to disclose. COPD Foundation receives 68% of annual funding from health care companies.

This page includes conflict of interest disclosures for ICER staff, external collaborators, and expert reviewers of the report. For all public meeting participant disclosures, please refer to Supplement I.

Table of Contents

List of Acronyms and Abbreviations Used in this Report

AEs	Adverse events
AHRQ	Agency for Healthcare Research and Quality
AIAN	American Indian or Alaskan Native
ATS	American Thoracic Society
CAR	Continuous Abstinence Rate
CDC	Centers for Disease Control and Prevention
CDR	Clinical Diversity Rating
CE	Cost-effectiveness
CI	Confidence interval
CO	Carbon monoxide
COPD	Chronic Obstructive Pulmonary Disease
CrI	Credible interval
CVD	Cardiovascular disease
CYT	Cytisinicline
ECDI	Electronic Cigarette Dependence Index
EQ-5D-5L	EuroQol-5 Dimension-5 Level
evLYs	Equal-value life years
FDA	Food and Drug Administration
FTND	Fagerström Test for Nicotine Dependence
HIDI	Health Improvement Distribution Index
HIV	Human immunodeficiency virus
IQR	Interquartile range
LYs	Life years
mg	Milligram
N	Number of participants
NA	Not applicable
NC	Not calculated
NH	Non-Hispanic
NHPI	Native Hawaiian or Pacific Islander
NMA	Network meta-analysis
NRT	Nicotine Replacement Therapy
OL	Open label
OR	Odds ratio
ORCA	Ongoing Research of Cytisinicline for Addiction trials
PDUFA	Prescription Drug User Fee Act
PP	Point Prevalence
ppm	Parts per million
QALY	Quality-adjusted life year
RCT	Randomized controlled trials
RR	Risk ratios
SAEs	Serious adverse events
SD	Standard deviation
TEAEs	Treatment-emergent adverse events
TID	Three times daily
VAR	Varenicline
VAREVAPE	Varenicline and Counseling for Vaping Cessation trial
ViVA	Varenicline for Nicotine Vaping Cessation in Adolescents trial

Executive Summary

Smoking cigarettes remains the number one cause of preventable deaths in the United States (US) with approximately half a million people dying each year from smoking-related illnesses.[1] The main smoking-related causes of death are cardiovascular (strokes and heart attacks), cancer (lung, pancreatic, esophageal, bladder, colorectal, renal, and other cancers), and pulmonary (chronic obstructive lung disease [COPD], pneumonia). The economic costs of smoking in the US were estimated to be more than $600 billion in 2018, including $240 billion in direct health care costs and $372 billion in lost productivity.[1,2] These costs do not include the cost of tobacco products to consumers, which was estimated to be $75.9 billion in 2021.[3]

There are several treatment approaches that have been shown to help people quit smoking. The two most effective medical therapies for smoking cessation available in the US are varenicline (previously Chantix®) and combination nicotine replacement therapy (NRT), a long-acting patch combined with short-acting nicotine gum or lozenges.[4]

Cytisinicline (cytisine) is derived from the seeds of an acacia bush; it has been used for smoking cessation for more than 50 years in Eastern Europe where it has historically been administered as a 1.5 mg tablet for 25 days using a downward titration schedule starting six times a day (100 tablets in total). Cytisine is a partial agonist of nicotinic acetylcholine receptors that helps to block the craving for cigarettes and blunts the short-term rewards that come from smoking a cigarette. This is essentially the same mechanism of action as varenicline. A new formulation from Achieve Life Sciences is a 3 mg pill given orally three times a day for 6 to 12 weeks. The Food and Drug Administration (FDA) Prescription Drug User Fee Act (PDUFA) date is June 20, 2026.

We performed a network meta-analysis (NMA) using two Phase III trials of the new formulation of cytisinicline to compare outcomes with varenicline. For other comparisons, we relied primarily on a 2023 Cochrane review.[4] Cytisinicline is substantially more effective than behavioral support alone: approximately 16 more people out of 100 trying to quit would succeed for six months with cytisinicline. The efficacy of cytisinicline appears similar to varenicline for both smoking cessation and to quit vaping nicotine, but there is uncertainty in these estimates. The 2023 Cochrane review found no significant difference between the older formulation of cytisinicline and either combination NRT or electronic cigarettes used for smoking cessation.

Varenicline has gastrointestinal (GI) side effects that can limit its tolerability and can produce vivid dreams that some people find disturbing. Cytisinicline has GI effects similar to placebo; it is unclear whether it causes less sleep disturbances than varenicline. In clinical trials, rates of discontinuation for adverse events (AEs) were not different between varenicline and cytisinicline.

Because of the lower rate of GI side effects, we rated cytisinicline as "comparable or incremental" (**C+**) compared with varenicline for smoking cessation. Other evidence ratings are shown in the table and explanations for these ratings can be found in Section 3.5 of this report.

Table ES1. Evidence Ratings

Treatment	Comparator	Evidence Rating
Adults Who Are Interested in Quitting Cigarettes		
Cytisinicline 3 mg TID with Behavioral Support	No pharmacotherapy/ behavioral support alone	A
	Varenicline	C+
	Combination NRT	C+
	Varenicline plus combination NRT	I
	Electronic cigarette with nicotine	I
	Bupropion	B+
Individuals Who Are Interested in Quitting Electronic Cigarettes (Vaping)		
Cytisinicline 3 mg TID with Behavioral Support	No pharmacotherapy/ behavioral support alone	C++
	Varenicline	P/I

mg: milligrams, NRT: nicotine replacement therapy, TID: three times a day

We developed an economic model focused on a hypothetical cohort of currently smoking patients who are interested in quitting cigarettes and who are being treated with one of three strategies at model entry: 1) cytisinicline with behavioral support, 2) varenicline with behavioral support, and 3) behavioral support alone. The model focused on the costs and harms of smoking.

With an FDA PDUFA date of June 20, 2026, the price of cytisinicline is currently not known. Our cost-effectiveness analysis was based on a placeholder price of $5,000 for a 12-week course. Under this assumption, cytisinicline meets commonly used thresholds for cost-effectiveness when compared with behavioral support alone but substantially exceeds these thresholds when compared with varenicline. Some analysts have suggested a lower estimated price for cytisinicline.

A potential additional benefit of cytisinicline not reflected in the comparative effectiveness or cost-effectiveness results is that some patients may be willing to try it for smoking cessation because it is a natural, plant-based product. Furthermore, any "new" therapy is likely to lead to some patients who previously were unable to quit smoking to make additional attempts. We also note that people living with serious psychiatric illness and those with low socioeconomic status are overrepresented in the population of current smokers in the US.

The Health Benefit Price Benchmark (HBPB) for cytisinicline is $1,900 to $2,700. For patients who have tried to quit smoking with varenicline and been unable to tolerate its gastrointestinal side effects, a somewhat higher price for cytisinicline might be appropriate.

At a placeholder price of $5,000 per treatment course, and estimated eligibility and uptake assumptions, approximately 4% of patients could be treated with cytisinicline over five years without exceeding ICER's budget impact threshold. At the lower end of ICER's threshold prices for cytisinicline ($1,200 per treatment course at $50,000 per QALY), approximately 20% of patients could be treated. Given the uncertainty in the actual price of cytisinicline and anticipated uptake, ICER is not issuing an access and affordability alert for cytisinicline.

Key Policy Recommendations:

The appraisal committee votes on questions of comparative effectiveness and value, along with key policy recommendations regarding pricing, access, and future research are included in the main report.

- The manufacturer of cytisinicline should set the price to align with the value of added patient benefits.
- All stakeholders have a responsibility to play in ensuring that an effective new treatment for patients who smoke is introduced in a way that will help reduce health inequities and stigma.
- Payers should ensure that benefit designs developed in conjunction with employers and other plan sponsors do not impose out-of-pocket requirements that create major barriers to appropriate access for patients.
- Regulators should provide an additional pathway for generic drug approval when the drug is approved elsewhere with extensive evidence of safety and efficacy outside the US.

1. Background

Smoking cigarettes remains the number one cause of preventable deaths in the United States (US).[3] Approximately half a million people die each year from smoking-related illnesses in the US. The main smoking-related causes of death are cardiovascular (strokes and heart attacks), cancer (lung, pancreatic, esophageal, bladder, colorectal, renal, and other cancers), and pulmonary (chronic obstructive lung disease [COPD], pneumonia). The economic costs of smoking in the US were estimated to be more than $600 billion in 2018, including $240 billion in direct health care costs and $372 billion in lost productivity.[1,2] These costs do not include the cost of tobacco products to consumers, which was estimated to be $75.9 billion in 2021.[3]

Since 1965, the percentage of Americans who smoke daily has declined from 42.6% to 11.6% in 2022.[5] The majority of daily smokers (68%) want to quit, and each year more than half try (53% in 2022), but fewer than 10% succeed.[5,6] Smoking in the US is more common in people who are male, middle-aged, White or Black, less educated, low-income, and suffer from psychological distress (Table 1.1).[2] Native Hawaiian/Pacific Islanders were not included in the referenced study, but they also have high rates of smoking (18.9% reported use in the past year in 2019).[7]

Table 1.1. Smoking Prevalence in 2022 in the United States by Selected Characteristics[2]

Characteristic	Percentage
Sex	
Male	13.1
Female	10.1
Age (Years)	
18-24	5.3
25-44	12.6
45-64	14.9
65+	8.3
Race/Ethnicity	
Asian	5.4
Black	11.7
Hispanic	7.7
White	12.9
Education	
GED	30.7
High School Diploma	17.1
Bachelor's Degree	5.3
Graduate Degree	3.2
Income	
Low	18.3
Middle	12.3
High	6.7
Psychological Distress	
Yes	28.1

Characteristic	Percentage
No	10.9

GED: General Educational Development

There are several treatment approaches that have been shown to help people quit smoking. Primary care providers are encouraged to ask all patients about tobacco use, advise those who smoke to stop smoking, and offer smoking cessation medications and counseling.[8] Smoking quit lines offer free counseling, and many smoking cessation centers offer in-person counseling as well. The two most effective medical therapies for smoking cessation available in the US are varenicline (previously Chantix®) and combination nicotine therapy (a long-acting patch combined with short-acting nicotine gum or lozenges). Other options include use of a single nicotine replacement therapy (NRT) product and bupropion (previously Zyban®).

The focus of this review is a potential new therapy, cytisinicline, also known as cytisine (Table 1.2). Cytisine is derived from the seeds of an acacia bush that grows in Eastern Europe. It has been used for smoking cessation, in a different formulation, for more than 50 years in Eastern Europe. Cytisine is a partial agonist of nicotinic acetylcholine receptors that helps to block the craving for cigarettes and blunts the short-term rewards that come from smoking a cigarette. This is essentially the same mechanism of action as varenicline. The formulation by Achieve Life Sciences is a 3 mg pill given orally three times a day for 6 to 12 weeks. The FDA PDUFA date is June 20, 2026.

Table 1.2. Interventions of Interest

Intervention	Mechanism of Action	Delivery Route	Prescribing Information
Cytisinicline	Partial agonist of the nicotinic acetylcholine receptor	Oral	3 mg by mouth three times a day

mg: milligrams

2. Patient Community Insights

During this review, we sought input from diverse stakeholders, including patients and patient advocates. This section incorporates insights gathered during calls with members of the patient community.

Patients' top three reasons for wanting to quit include worries about current and future health, cost, and not liking the feeling of being addicted. They told us how challenging it is to quit smoking. It is important to grasp how terribly addictive smoking is, both the chemical dependence as well as the social and psychological factors. Some smokers have no interest in quitting regardless of the consequences to their health. One patient with a smoking-related cancer diagnosis had tried everything. She tried both in-person and telephone-based counseling. She found herself smoking while using the nicotine patch and thought that was a problem for her health. She tried nicotine lozenges, but they tasted horrible to her. She was prescribed Chantix, but friends told her that Chantix causes terrible nightmares, so she never tried it. She even tried electronic cigarettes, but they cost even more than cigarettes, so she went back to cigarettes.

Stress and environmental triggers were common themes. One patient tried many times to quit, but stressors triggered relapses. The only time that she was able to successfully quit was when she moved to a different state, away from triggers in her environment. However, once she returned home, the same triggers were present, and she started smoking again.

One of the many challenging aspects of tobacco addiction is the stigma. "There's so much stigma against smoking. More so than with other lifestyle choices that also aren't great, but they don't carry as much stigma." Many times, patients blame themselves. They say, "This is my fault. I've made myself sick."

Another patient said that she knows that she needs to quit, but she was very concerned about the associated weight gain and mood swings. Another said, "I finally had to just put sticky notes all over the place and tell myself, you've got to become a non-smoker." She saw her mother die with COPD, and her father also died with heart issues because of smoking. "We think we know better, but it's a horrible habit, and it's very, very hard to break."

One patient's routine includes smoking for relaxation. If she has trouble sleeping, she gets up and goes out on her porch with her cat to have a cigarette. Then she can fall back asleep. She finds it hard to give up this routine.

Vaping is particularly challenging. Smoking has a built-in barrier to easy use: lighting the cigarette. This is what makes vaping different: vaping is that much more accessible. Some patients say vaping is the first thing they do in the morning and the last thing they do at night. In addition, the solution that is being vaped can be very high in nicotine as well. Patients who vape often consume much higher amounts of nicotine than cigarette smokers.

We heard from patients struggling to quit vaping. One patient had tried both nicotine patches and gum to help curb his appetite for nicotine while at work, but they didn't help him to quit. He expressed a lack of motivation to quit at the time, as well as feeling embarrassed to vape at work. In the end, not wanting to vape while out on dates provided the motivation to help him quit.

One patient who used electronic cigarettes noted how hard it was to be dependent on nicotine. He felt as though his brain was being squeezed. He found it hard to concentrate without nicotine. Eventually, once he was committed to quitting, nicotine patches helped him to quit, along with apps that offered behavioral rewards for his progress in quitting.

3. Comparative Clinical Effectiveness

3.1. Methods Overview

Procedures for the systematic literature review are described in Supplement D1. A research protocol was published on Open Science Framework and is registered with PROSPERO (CRD420251072845). Our literature search was conducted in June 2025 and updated in November 2025.

Scope of Review

Our review assessed the clinical effectiveness and safety of cytisinicline used in conjunction with behavioral support. We focused on evaluating how well these therapies help individuals quit smoking, which we consider an adequate surrogate for health benefits. However, we are less certain whether this surrogate applies equally to electronic cigarettes/vaping cessation. We included six comparisons of cytisinicline against other pharmacotherapies and devices in individuals who are interested in quitting smoking:

1. What is the net health benefit of cytisinicline with behavioral support compared to no pharmacotherapy/behavioral support alone?

2. What is the net health benefit of cytisinicline with behavioral support compared to varenicline plus behavioral support?

3. What is the net health benefit of cytisinicline with behavioral support compared to varenicline plus nicotine replacement therapy (NRT) and behavioral support?

4. What is the net health benefit of cytisinicline with behavioral support compared to NRT products (e.g., nicotine patch plus a short-acting NRT such a gum or lozenge) plus behavioral support?

5. What is the net health benefit of cytisinicline with behavioral support compared to electronic cigarettes containing nicotine (for smoking cessation) plus behavioral support?

6. What is the net health benefit of cytisinicline with behavioral support compared to bupropion plus behavioral support?

We also looked at the available evidence among those looking to quit nicotine electronic cigarettes (vaping), which generated two additional research questions:

1. What is the health benefit of cytisinicline with behavioral support compared to no pharmacotherapy or behavioral support alone?

2. What is the net health benefit of cytisinicline with behavioral support compared to varenicline plus behavioral support?

Outcomes of interest included abstinence from cigarette smoking or a decrease in cigarettes smoked, tolerability of treatment (e.g., discontinuation from treatment due to adverse events, and harms (e.g., insomnia, nausea, etc.).

The full scope of the review is described in Supplement Section D1.

Evidence Base

Cytisinicline for Smoking Cessation

Cytisinicline Pivotal Trials (ORCA)

Cytisinicline has historically been administered as a 1.5 mg tablet for 25 days using a downward titration schedule starting six times a day (100 tablets in total). Its efficacy, effectiveness and safety has been previously covered in other systematic reviews.[4,9] A simpler treatment regimen, cytisinicline 3 mg three times a day (TID), was first studied in a Phase II study, ORCA-1.[10]

The pivotal Phase III trials of cytisinicline, ORCA-2 and 3, studied cytisinicline 3 mg TID with behavior support compared to placebo with behavioral support.[11,12] For this review, we focused on the 12-week cytisinicline course as it was superior to the six-week course and matches the recommended treatment duration of varenicline.

The trials enrolled adult daily smokers of at least 10 cigarettes who intended to quit within a week and had made at least one prior quit attempt. The studies excluded participants with recent drug use, recent serious cardiovascular events, psychosis or bipolar disorder, current suicidal risk, or moderate to severe depression. Across the two trials (Supplement Table D3.2), participants were on average in their early 50s, about half were female (52.7%), and largely White (79.6%) or Black/African American (17.9%). On average, the trial population smoked a pack a day for over 30 years and were moderately dependent on nicotine. They had a median of four quit attempts with nicotine patches/gum/lozenges, varenicline, or bupropion. The primary outcome was biochemically confirmed smoking cessation from weeks 9 to 12, with sustained abstinence to week 24 as a secondary outcome. Drug tolerability and common harms were also reported.

We performed a fixed effects meta-analysis of the two ORCA trials to summarize the direct evidence of cytisinicline against behavioral support alone. Results are presented as risk ratios (RR) and absolute treatment differences. We provide additional methodological details of the meta-analysis in Supplement Section D2 and present comparisons against the random-effects model in Supplement Table D2.1. We also performed a network meta-analysis (NMA) of the primary clinical trials of the new formulation, cytisinicline, against varenicline.

Varenicline Trials Contributing to ICER's Network Meta-Analysis

In addition to the ORCA-2 and 3 studies, we identified 20 randomized trials of varenicline + behavioral support for 12 weeks in patients with similar inclusion/exclusion criteria. Baseline characteristics and risk of bias assessments for the included studies are summarized in Supplement Tables D2.3 and D1.4.

Systematic Reviews and Other New Evidence

Currently, there are no head-to-head trials comparing the 12-week regimen of 3 mg TID cytisinicline with other common smoking cessation treatments (combination NRT, varenicline plus combination NRT, electronic cigarettes, and bupropion). We used a comprehensive 2023 Cochrane Review ("Pharmacological and electronic cigarette interventions for smoking cessation in adults: component network meta-analyses") as our primary source for indirect treatment comparisons of cytisinicline versus these comparators.[4] The cytisinicline studies in the NMAs predominantly involved the older 25-day treatment course. For consistency, we reported all odds ratios (OR) as cytisinicline versus the comparator. We supplemented the Cochrane NMA results with a qualitative review of new evidence published since their search to answer Research Questions 3 to 6.

Varenicline plus combination NRT (e.g., nicotine patch plus a short-acting NRT such as gum or lozenge) was not a component in the Cochrane review. Our literature search did not identify any relevant randomized controlled trials (RCTs) evaluating this treatment combination. Previous studies have tested varenicline with either a nicotine patch or fast-acting NRT, which are not optimal uses of NRT, and have found mixed study results of increased smoking cessation rates over varenicline monotherapy.[13] As such, we were unable to provide a reliable comparison.

One additional RCT of bupropion versus placebo among smokers with Human Immunodeficiency virus (HIV) was identified; its findings were consistent with the summary estimates in the Cochrane review.[14]

Electronic cigarettes are not approved by the FDA for smoking cessation. However, they have been studied for smoking cessation and are used by some patients to stop smoking cigarettes. The Cochrane NMA included 16 RCTs of electronic cigarettes with nicotine for smoking cessation. A review of the 2023 Cochrane review, a 2025 Cochrane review specific to electronic cigarettes, and 15 other systematic reviews was also assessed, which included a total of 24 RCTs evaluating electronic cigarettes for smoking cessation.[4,15,16]

Vaping Cessation

We identified three relevant RCTs evaluating cytisinicline or varenicline in individuals trying to quit electronic cigarettes. ORCA V-1 was a Phase II trial that randomized 160 adult daily users of electronic cigarettes to a 12-week course of cytisinicline (n=106) or placebo (n=53); brief vaping-cessation counseling.[17] This trial included participants across five US states who averaged 33 years of age. The majority had a history of cigarette smoking (79%) but were abstinent at least 30 days prior to enrollment. The primary study outcome was continuous electronic cigarette abstinence from weeks 9 to 12. Other outcomes included sustained abstinence rates between weeks 3 to 6, 6 to 9, and 9 to 16, plus seven-day point prevalence estimates and saliva cotinine levels throughout 16 weeks of follow-up.

The ViVa study randomized 216 individuals (aged 16 to 25 years) in Boston, Massachusetts, to a 12-week course of varenicline or placebo. All patients received behavioral counseling.[18] Study participants had an average age of 21 years. Less than 10% had smoked cigarettes in the 30 days prior to enrollment. The primary outcome was continuous abstinence from weeks 9 to 12, with additional measurements from weeks 9 to 24. Other outcomes included point prevalence abstinence throughout 24 weeks, reductions in nicotine and vaping craving, and mood and anxiety symptoms.

The VAREVAPE study randomized 140 participants to 12 weeks of varenicline or placebo; all participants received behavioral support.[19] Study participants were recruited in Italy, and on average were in their 50s, had a 27-year history of cigarette smoking, and two years of vaping. The primary study endpoint was continuous vaping abstinence from weeks 4 to 12, with an additional assessment between weeks 4 and 24. Additional outcomes included seven-day point prevalence estimates throughout 24 weeks of follow-up.

Participants in all three trials reported a medium to high dependence on electronic cigarettes as measured by the Penn State Electronic Cigarette Dependence index. (See Supplement Table D3.4 for details).

3.2. Clinical Benefits

Smoking Cessation

Cytisinicline

We estimate that 23 (95% CI: 19 to 28) additional smokers per 100 people may quit smoking in the last four weeks of their 12-week treatment course of 3 mg TID cytisinicline plus behavioral support, compared to behavioral support alone. Across a longer follow-up through six months (24 weeks), an estimated 16 more smokers (95% CI: 12 to 20) are likely to quit with cytisinicline. These absolute risk differences translate into a risk ratio of 3.8 and 4.6, respectively.

Table 3.1. Meta-Analysis of Smoking Abstinence, 12-Week Cytisinicline + Behavioral Support Compared to Behavioral Support Alone[11,12]

Trial	ORCA-2		ORCA-3		Meta-Analysis Results Absolute Risk & Relative Risk Difference (95% Confidence Interval)
Arms*	12-Week Cytisinicline	12-Week Placebo	12-Week Cytisinicline	12-Week Placebo	
N	270	271	264	265	
Primary Outcome: Continuous Abstinence from Weeks 9 to 12, %	32.6	7.0	30.3	9.4	Risk Difference: 0.23 (0.19, 0.28) Risk Ratio: 3.83 (2.81, 5.22)
Secondary Outcome: Continuous Abstinence from Weeks 9 to 24, %	21.1	4.8	20.5	4.2	Risk Difference: 0.16 (0.12, 0.20) Risk Ratio: 4.64 (3.04 to 7.1)

CI: confidence interval, N: number, ORCA: ongoing research of cytisinicline for addiction trials
*All arms were provided with behavioral support.

Subgroup Analyses and Heterogeneity

A subgroup analysis of ORCA-2 study results is presented in Supplement Table D6.1. There was no evidence of effect modification by subgroups of age, gender, or history of prior quit attempts. For participants who smoked 20 or fewer cigarettes per day, the odds of quitting smoking at the end of treatment with cytisinicline compared to placebo was 10.2 (95% CI: 3.41 to 30.50), which was numerically higher than the odds ratio of 5.40 (95% CI: 2.92 to 10.00) observed in participants who smoked more than 20 cigarettes per day. However, this difference was not statistically significant (p=0.321). A post-hoc analysis of ORCA-2 and 3 studies found no difference in treatment effect between smokers with and without self-reported COPD; the smoking quit rates were lower in both treatment and placebo arms among COPD smokers versus non-COPD smokers.[20] Data on the remaining subgroups of interest were not available.

Cytisinicline With Behavioral Support Versus Varenicline Plus Behavioral Support

To date, there are no head-to-head trials evaluating the updated 3 mg TID 12-week treatment course of cytisinicline against varenicline. Thus, we conducted an NMA to indirectly compare the two treatments on the outcomes of smoking cessation (continuous abstinence rate across weeks 9 to 24), tolerability (treatment discontinuation due to adverse events), and commonly known harms (e.g., nausea, headache). Due to the heterogeneity of the trials and improved model fit, our primary analysis employed random-effects NMAs and presented results using relative risk ratios (RR) and absolute treatment differences. See Supplement Section D2 for additional methodology and data inputs of the NMA.

An NMA comparison between cytisinicline and varenicline, both as add-ons to behavioral support, found no statistically significant treatment difference, with a risk ratio of 1.1 (95% CrI: 0.76 to 1.7) and absolute risk difference of 0.03 (95% CrI: -0.06 to 0.18).

Table 3.2. Continuous Abstinence From Weeks 9 to 24 NMA (Risk Ratio)

CYT 12-Week + Behavioral Support		
1.1 (0.76 to 1.7)	VAR 12-Week + Behavioral Support	
2.71 (1.91 to 4.02)	2.45 (2.19 to 2.71)	Behavioral Support Alone

CYT: cytisinicline, VAR: varenicline

Table 3.3. Continuous Abstinence From Weeks 9 to 24 NMA (Absolute Risk Difference)

CYT 12-Week + Behavioral Support		
0.03 (-0.06 to 0.18)	VAR 12-Week + Behavioral Support	
0.18 (0.10 to 0.32)	0.15 (0.13 to 0.18)	Behavioral Support Alone

CYT: cytisinicline, VAR: varenicline

These results are in line with previous systematic reviews comparing the two therapies; we provide an overview of several of these reviews in Supplement Section D5**.**

Cytisinicline With Behavioral Support Versus Other Comparators

The 2023 Cochrane review found no significant difference in smoking abstinence at six months or more between cytisinicline and combination NRT (OR 1.15; 95% CrI: 0.83 to 1.59) or between cytisinicline and electronic cigarettes (OR 0.94; 95% CrI: 0.62 to 1.43).[4] However, cytisinicline showed higher odds of cessation than bupropion (OR 1.55; 95% CrI: 1.16 to 2.09), with about four more quitters per 100 smokers.[4]

Vaping Cessation

On the primary outcome of continuous abstinence from electronic cigarettes from weeks 9 to 12, people who vape and are taking cytisinicline were more likely to maintain abstinence than those provided behavioral support alone (OR 2.64, 95% CI 1.07 to 7.1, p=0.04). Compared to behavioral support alone, cytisinicline was associated with higher odds of continuous abstinence rates across follow-up periods of weeks 3 to 6, weeks 6 to 9, and weeks 9 to 16, but these differences were not statistically significant (Table 3.4).

Table 3.4. ORCA V-1 Continuous Electronic Cigarette Abstinence Results[17]

Arms*		12-Week Cytisinicline (n=107)	12-Week Placebo (n=53)	Odds Ratio (95% CI), p-Value
Continuous Abstinence Rate, n (%)	Weeks 9-12†	34 (31.8)	8 (15.1)	**2.64 (1.07-7.10), 0.04**
	Weeks 3-6‡	26 (24.3)	8 (15.1)	1.81 (0.77-4.55), 0.22
	Weeks 6-9‡	33 (30.8)	9 (17.0)	2.18 (0.97-5.20), 0.09
	Weeks 9-16	25 (23.4)	7 (13.2)	2.00 (0.82-5.32), 0.15

CI: confidence interval, n: number

*All arms were administered with behavioral support.

†Primary outcomes: electronic cigarette abstinence reported and validated at weeks 9, 10, 11, and 12.

‡Secondary outcomes: electronic cigarette abstinence reported and validated at weeks 3, 4, 5 and 6 or at weeks 6, 7, 8, and 9.

Subgroup Analyses and Heterogeneity

A subgroup analysis of ORCA-V1 found no treatment effect modification by age, sex, race, or baseline nicotine dependence (Supplement Table D6.2).

Network Meta-Analysis

We conducted a random-effects NMA of three placebo-controlled studies evaluating a 12-week course of cytisinicline or varenicline plus behavioral support in adults looking to quit vaping (Table 3.5). Our outcome of interest, continuous vaping abstinence across weeks 9 to 24 of follow-up, was unavailable across the three trials. Instead, we opted to use seven-day point prevalence measured at the longest available follow-up of 12 weeks.

Both cytisinicline (RR 1.65; 95% CrI: 0.22 to 12.78) and varenicline (RR 2.3; 95% CrI: 0.55 to 9.54) increased the rates of quitting compared to behavioral support alone. However, there was no difference in seven-day abstinence rates at 12 weeks between cytisinicline and varenicline (RR 0.72; 95% CrI: 0.06 to 8.78) (Table 3.5).

Given the wide credible intervals of each point estimate, we have low certainty in these results. As reported above, both therapies have demonstrated an increased likelihood of smoking cessation

over no pharmacotherapy, and we believe these benefits are likely to carry over to nicotine addiction in users of electronic cigarettes.

Results from a planned larger Phase III trial, ORCA V-2, will provide greater statistical power and insight into cytisinicline's benefit among individuals looking to quit vaping (Supplement Table D4.1).

Table 3.5. NMA Results- 7-Day Point Prevalence at Week 12- Risk Ratio (95% Credible Interval) Random Effects Model

CYT 12-Week + Behavioral Support		
0.72 (0.06, 8.78)	VAR 12-Week + Behavioral Support	
1.65 (0.22, 12.78)	2.3 (0.55, 9.54)	Behavioral Support Alone

CYT: Cytisinicline, VAR: Varenicline

3.3. Harms

Cytisinicline 3 mg TID

We present the likelihood of six tolerability and safety events among smokers treated with cytisinicline 3 mg TID versus placebo/behavioral support alone (Table 3.6). Overall, cytisinicline appears to be a well-tolerated and safe medication when taken three times daily for 12 weeks.

Treatment with cytisinicline is associated with a higher risk of insomnia and abnormal dreams. The data indicate no increased risk for all other common adverse events. A review of safety events in the vaping ORCA V-1 study found no new safety signals; a 12-week course of cytisinicline resulted in a greater incidence of abnormal dreams (12.3% vs. 1.9%) and insomnia (10.4% vs. 1.9%) than placebo. All other adverse events were at a similar frequency to placebo. An overview of the meta-analysis results, with calculated risk ratios for each outcome, is provided in Supplement Table D3.3.

Table 3.6. Key Tolerability and Safety Events of Cytisinicline 3 mg TID + Behavioral Support Versus Placebo/Behavioral Support Alone[11,12]

ORCA-2 and -3 (Pooled Arms)			
	12-Week Cytisinicline (N=530)	**12-Week Placebo (N=532))**	**Meta-Analysis (Fixed Effects)Absolute Risk Difference (95% CI)**
Headache	43 (8)	38 (7)	0.01 (-0.02, 0.04)
Nausea	33 (6)	38 (7)	-0.01 (-0.04, 0.02)
Insomnia	57 (11)	33 (6)	**0.05 (0.01, 0.08)**
Abnormal Dreams	41 (8)	28 (5)	**0.03 (0.01, 0.06)**
Discontinuation Due to AEs, n (%)	15 (3)	7 (1)	0.02 (-0.00, 0.03)
Serious AEs, n (%)	16 (3)	11 (2)	0.01 (-0.01, 0.03)

AEs: adverse events, CI: confidence interval, N: number, TEAEs: treatment-emergent adverse events

On September 3, 2025, the manufacturer issued a press release announcing that the New Drug Application includes long-term safety data from over 400 participants exposed to cytisinicline for at least six months and over 200 participants exposed for at least one year, with no new safety concerns reported (Supplement Table D4.1).[21]

Varenicline

An indirect comparison of cytisinicline against varenicline on safety events is presented in Table 3.7. Evidence from the NMA suggests that smokers treated with cytisinicline are at a lower risk of nausea than those treated with varenicline, although this did not translate into fewer discontinuations due to adverse events. All other comparisons were not statistically significant.

Table 3.7. Network Meta-Analysis of Key Tolerability and Safety Events, Cytisinicline Versus Varenicline 12-Week Treatment, Random Effects Model

		Overall Effect Estimates, Risk Ratio (95% CrI)	Absolute Risk Difference (95% CrI)
Most Frequent TEAEs	**Headache**	0.84 (0.56, 1.32)	-0.02 (-0.06, 0.04)
	Nausea	**0.24 (0.16, 0.35)**	**-0.21 (-0.25, -0.18)**
	Insomnia	1.2 (0.69, 2.06)*	0.03 (-0.05, 0.14)*
	Abnormal Dreams	0.68 (0.4, 1.17)	-0.04 (-0.08, 0.02)
Discontinuation Due to AEs		1.31 (0.5, 3.61)*	0.01 (-0.03,0.11)*
Serious AEs		1.53 (0.67, 3.66)*	0.01 (-0.01, 0.05)*

AEs: adverse events, CrI: credible interval, n: number, TEAEs: treatment-emergent adverse events
Note: All arms were administered with behavioral support.
*Not adjusted for baseline risk due to model fit assessment in Supplement Table D2.9

Varenicline previously had an FDA black box warning for serious neuropsychiatric events (e.g., suicidality, depression, and aggression) from 2009 to 2016.[22] The EAGLES trial studied 8,144 participants, with and without psychiatric conditions, and found no significant increase in these events compared to nicotine patches or placebo. Subsequently, the black box warning was removed.

Combination Nicotine Replacement Therapy (NRT) Products (e.g., Nicotine Patch Plus a Short-Acting NRT Such a Gum or Lozenge)

The 2023 Cochrane review found no significant differences in serious adverse events (OR 0.91; 95% CrI: 0.49 to 1.69) or treatment-related withdrawals (OR 0.60; 95% CrI: 0.28 to 1.35) for cytisinicline compared to combination NRT.

Overall, NRT products have a favorable safety and tolerability profile, with side effects that are manageable and transient. These include local skin reactions (patch), mouth irritation (gum or

lozenge), and other mild symptoms (e.g., abnormal dreams, nausea, insomnia). There does not appear to be an increased risk of nicotine toxicity with combination therapy over single product use.[23]

Electronic Cigarettes Containing Nicotine (For Smoking Cessation)

The 2023 Cochrane review estimated an increased risk of serious adverse events with cytisinicline compared to electronic cigarettes (OR 1.19; 95% CrI: 0.62 to 2.27), but this difference was not statistically significant. No data on withdrawal due to adverse events were reported.

Short-term electronic cigarette use is associated with throat or mouth irritation, headache, cough, and nausea, which generally decrease with continued use.[4] While they are less harmful than traditional cigarettes, electronic cigarettes still carry some risks as they can expose individuals to toxic substances.[24] No electronic cigarette product has sought FDA regulatory approval as a medical product, raising concerns about safety and the potential for unidentified risks, particularly with years of regular use.

The long-term safety of electronic cigarettes remains uncertain. Although vaping delivers fewer carcinogens and toxicants than smoking, it may still increase risks of DNA damage and mutagenesis, COPD, and asthma exacerbation.[24,25]

Bupropion

Findings from the 2023 Cochrane review found no statistically significant difference in the likelihood of serious adverse events between cytisinicline and bupropion, with an estimated OR (95% credible interval) of 0.69 (0.38 to 1.22). Likewise, there was no significant difference between therapies on the risk of withdrawal due to adverse events (OR 0.80; 95% CI: 0.42 to 1.55).

Bupropion is contraindicated in patients with a history of seizures because it lowers the seizure threshold.[26] Gradual dosing of the drug up to 300 mg a day (two 150 mg tablets) is recommended to reduce the risk of seizures. The absolute risk of seizures in patients receiving 300 mg per day is low (0.1%). More common adverse events associated with the drug include insomnia, rhinitis, dry mouth, dizziness, nervous disturbance, anxiety, nausea, constipation, and arthralgia.

3.4. Uncertainty and Controversies

- Cytisinicline and varenicline are closely related medications and appear to have similar effects on smoking cessation. In the absence of head-to-head trials with the formulation submitted to the FDA, indirect comparisons are unlikely to be able to conclusively answer whether one of these two medications has greater efficacy than the other.

- There is uncertainty about the optimal duration of therapy for cytisinicline. Studies found that 12 weeks of treatment was superior to six weeks. It is possible that longer therapy would be even more effective because it both decreases cravings and blunts the rewards of nicotine. Additionally, varenicline, which shares the same mechanism of action as cytisinicline, is often used for longer than 12 weeks. Long-term safety data submitted to the FDA apparently suggest no safety concerns when cytisinicline is taken for at least one year.[21]

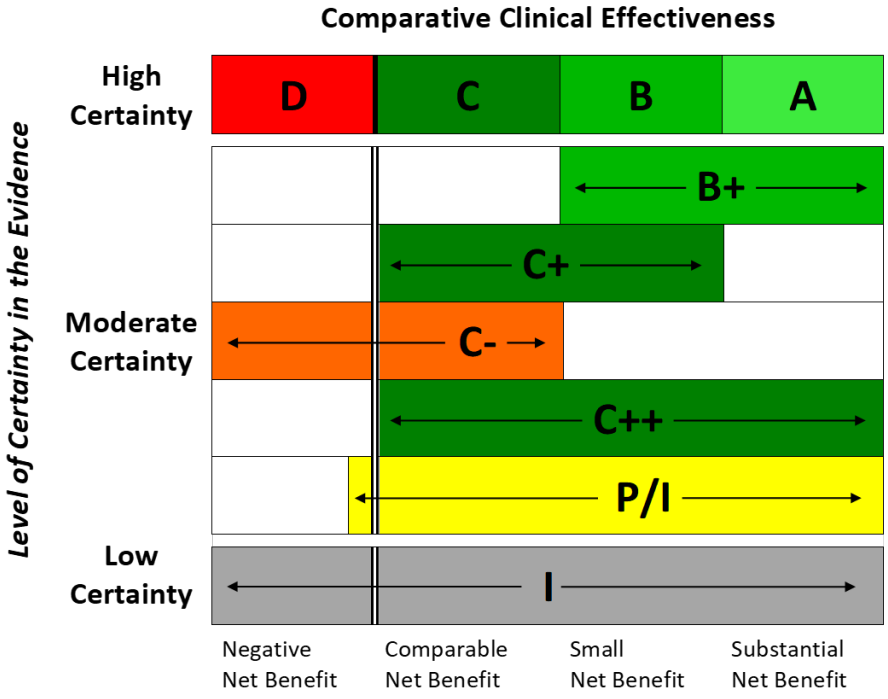
- Patients with serious mental health disorders were excluded from the US cytisinicline clinical trial program. Such patients are overrepresented among people who smoke in the US and typically have more difficulty with smoking cessation. The exclusion of these patients limits information on the efficacy of cytisinicline in an important population.

- There is limited evidence about the clinical benefits of cytisinicline in people who vape nicotine. While a pilot study suggests that cytisinicline may assist with quitting vaping, further study is needed. Additionally, the harms of vaping remain controversial, so the health benefits of quitting vaping are uncertain.

3.5. Summary and Comment

An explanation of the ICER Evidence Rating Matrix (Figure 3.1) is provided here.

Figure 3.1. ICER Evidence Rating Matrix



A = "Superior" - *High certainty of a substantial (moderate-large) net health benefit*
B = "Incremental" - *High certainty of a small net health benefit*
C = "Comparable"- *High certainty of a comparable net health benefit*
D= "Negative"- *High certainty of an inferior net health benefit*
B+= "Incremental or Better" – *Moderate certainty of a small or substantial net health benefit, with high certainty of at least a small net health benefit*
C+ = "Comparable or Incremental" - *Moderate certainty of a comparable or small net health benefit, with high certainty of at least a comparable net health benefit*
C- = "Comparable or Inferior" – *Moderate certainty that the net health benefit is either comparable or inferior with high certainty of at best a comparable net health benefit*
C++ = "Comparable or Better" - *Moderate certainty of a comparable, small, or substantial net health benefit, with high certainty of at least a comparable net health benefit*
P/I = "Promising but Inconclusive" *- Moderate certainty of a small or substantial net health benefit, small (but nonzero) likelihood of a negative net health benefit*
I = "Insufficient" – *Any situation in which the level of certainty in the evidence is low*

The evidence ratings for all the comparisons specified in our research questions are summarized in Table 3.8 below.

Direct evidence from two randomized trials at low risk of bias found that treatment with cytisinicline 3 mg TID and behavioral support for 12 weeks led to sustained smoking cessation through 24 weeks in 16 more smokers per 100 treated compared with behavioral support alone (95% CI: 12 to 20). Side effects were generally mild (insomnia, abnormal dreams). There were

nominally more discontinuations due to AEs in the cytisinicline group (3% vs. 1%), but the percentages were low. Smoking has serious harms and quitting smoking has clear health benefits. There is high certainty of substantial net health benefit for cytisinicline compared with behavioral support alone (A, Superior).

Indirect evidence from two randomized trials of cytisinicline 3 mg TID and 20 randomized trials of varenicline, all for 12 weeks of active therapy, found similar rates of continuous abstinence through 24 weeks (RR 1.1; 95% CrI: 0.8 to 1.7). Overall, side effects were similar. Although cytisinicline had lower rates of nausea (RR 0.24; 95% CrI: 0.16 to 0.35), rates of discontinuation due to AEs were similar (RR 1.3; 95% CrI: 0.5 to 3.6) and low for both therapies. There is moderate certainty of comparable or a small net health benefit for cytisinicline compared with varenicline, with high certainty of at least comparable net health benefits (C+, comparable or incremental).

Indirect evidence from the Cochrane 2023 review found similar rates of long-term smoking cessation for cytisinicline compared with combination NRT and found similar harms. There is moderate certainty of comparable or a small net health benefit for cytisinicline compared with combination NRT, with high certainty of at least comparable net health benefits (C+, comparable or incremental).

There is insufficient evidence (I) to assess the net health benefit of cytisinicline compared with varenicline plus combination NRT. The certainty of evidence is low because none of the studies in our network included varenicline plus combination NRT, so we have only very low quality evidence for this comparison.

There is insufficient evidence (I) to assess the net health benefit of cytisinicline compared with electronic cigarettes. Indirect evidence from the Cochrane 2023 review found similar rates of long-term smoking cessation for cytisinicline compared with electronic cigarettes and found similar harms. However, the certainty of evidence is low because of the uncertainty about the long-term harms of electronic cigarette use.

Indirect evidence from the Cochrane 2023 review found a higher rate of long-term smoking cessation for cytisinicline compared with bupropion (OR 1.55; 95% CrI: 1.16 to 2.09). The rates of harms were similar, though there were trends in favor of cytisinicline. There is moderate certainty of a small or substantial net health benefit for cytisinicline compared with bupropion, with high certainty of at least a small net health benefit (B+, incremental or better).

Direct evidence from one small, randomized trial at low risk of bias found that treatment with cytisinicline 3 mg TID and behavioral support for 12 weeks led to sustained cessation of electronic cigarettes through 12 weeks compared with behavioral support alone. Side effects were generally mild (insomnia, abnormal dreams). A larger Phase III trial is currently enrolling patients. Harms of vaping nicotine are uncertain. There is moderate certainty of comparable, small, or substantial net

health benefit for cytisinicline compared with behavioral support alone (C++, Superior) for cessation of electronic cigarettes.

Indirect evidence from the one small, randomized trial of cytisinicline 3 mg TID and two randomized trials of varenicline for electronic cigarette cessation found similar rates of continuous abstinence through 12 weeks (RR 0.7; 95% CrI: 0.2 to 3.0). Credible intervals were very wide. As with these two therapies for smoking cessation, the side effects were similar. There is moderate certainty of a small or substantial net health benefit for cytisinicline compared with varenicline for electronic cigarette cessation, but also a small possibility of net harm (P/I, promising, but inconclusive).

Table 3.8. Evidence Ratings

Treatment	Comparator	Evidence Rating
Adults Who Are Interested in Quitting Cigarettes		
Cytisinicline 3 mg TID with Behavioral Support	No pharmacotherapy/ behavioral support alone	A
	Varenicline	C+
	Combination NRT	C+
	Varenicline plus combination NRT	I
	Electronic cigarette with nicotine	I
	Bupropion	B+
Individuals Who Are Interested in Quitting Electronic Cigarettes (Vaping)		
Cytisinicline 3 mg TID with Behavioral Support	No pharmacotherapy/ behavioral support alone	C++
	Varenicline	P/I

A: "Superior" High certainty of a substantial (moderate-large) net health benefit, B+: "Incremental or Better" Moderate certainty of a small or substantial net health benefit with high certainty of at least a small net health benefit, C+: "Comparable or Incremental" Moderate certainty of a comparable or a small net health benefit with high certainty of at least a comparable net health benefit, I: "Insufficient" Any situation in which the level of certainty in the evidence is low, mg: milligrams, NRT: nicotine replacement therapy, P/I: "Promising but Inconclusive" Moderate certainty of a small or substantial net health benefit and/or small (but nonzero) likelihood of a negative net health benefit, TID: three times a day

Midwest CEPAC Votes

Table 3.9. Midwest CEPAC Votes on Comparative Clinical Effectiveness Questions

Question	Yes	No
For people who smoke cigarettes, is the current evidence adequate to demonstrate that the net health benefit of cytisinicline is greater than that of behavioral support alone?	14	0
For people who smoke cigarettes, is the current evidence adequate to demonstrate that the net health benefit of cytisinicline with behavioral support is greater than that of varenicline with behavioral support?	1	13
For people who smoke cigarettes, is the current evidence adequate to demonstrate that the net health benefit of cytisinicline with behavioral support is greater than that of electronic cigarettes containing nicotine with behavioral support?	0	14
For people who vape nicotine, is the current evidence adequate to demonstrate that the net health benefit of cytisinicline with behavioral support is greater than that of behavioral support alone?	6	8
For people who vape nicotine, is the current evidence adequate to demonstrate that the net health benefit of cytisinicline with behavioral support is greater than that of varenicline with behavioral support?	1	13

The council unanimously voted that the current evidence is adequate to demonstrate that the net health benefit of cytisinicline is greater than that of behavior support alone for people who smoke. During deliberation, council members discussed the efficacy, side effects, and dose frequency of cytisinicline.

A large majority of the council voted that the current evidence is not adequate to demonstrate that the net health benefit of cytisinicline with behavioral support is greater than that of varenicline with behavioral support.

The council unanimously voted that the current evidence is not adequate to demonstrate that the net health benefit of cytisinicline with behavioral support is greater than that of electronic cigarettes with behavioral support. In reaching this conclusion, the council considered clinical perspectives on electronic cigarettes in the United States and the United Kingdom, as well as uncertainty regarding its comparative effectiveness for smoking cessation.

A slight majority of the council voted that the current evidence is not adequate to demonstrate that the net health benefit of cytisinicline with behavioral support is greater than that of behavioral support alone for people who vape nicotine.

During deliberation, one council member shared that they voted in the minority, reasoning that cytisinicline treats the nicotine addiction itself rather than the delivery mechanism, and therefore its benefits should translate to people who vape, even if to a lesser degree. Another member voted in the majority, sharing that while there may be a signal of benefit, the key word that influenced his vote is whether the evidence is adequate to demonstrate net health benefit.

The majority of the council voted that the current evidence does not adequately demonstrate that the net health benefit of cytisinicline with behavioral support is greater than that of varenicline with behavioral support for people who vape nicotine.

4. Long-Term Cost Effectiveness

4.1. Methods Overview

We developed a *de novo* decision analytic model for this evaluation, informed by key clinical trials and prior relevant economic models, with primary reference to the published BENESCO model that was used to assess the cost-effectiveness of varenicline.[27] Costs and outcomes were discounted at 3% per year.[27]

The model focused on an intention-to-treat analysis, with a hypothetical cohort of currently smoking patients who are interested in quitting cigarettes and who are being treated with one of three strategies at model entry: 1) cytisinicline with behavioral support, 2) varenicline with behavioral support, and 3) behavioral support alone, entering the model. Model cycle length was three months to reflect the treatment duration and follow-up times observed in the pivotal clinical trials of cytisinicline.[11,12] Half-cycle corrections were used to reflect the continuous nature of changes in patient characteristics and health state transitions over the lifetime of the model.

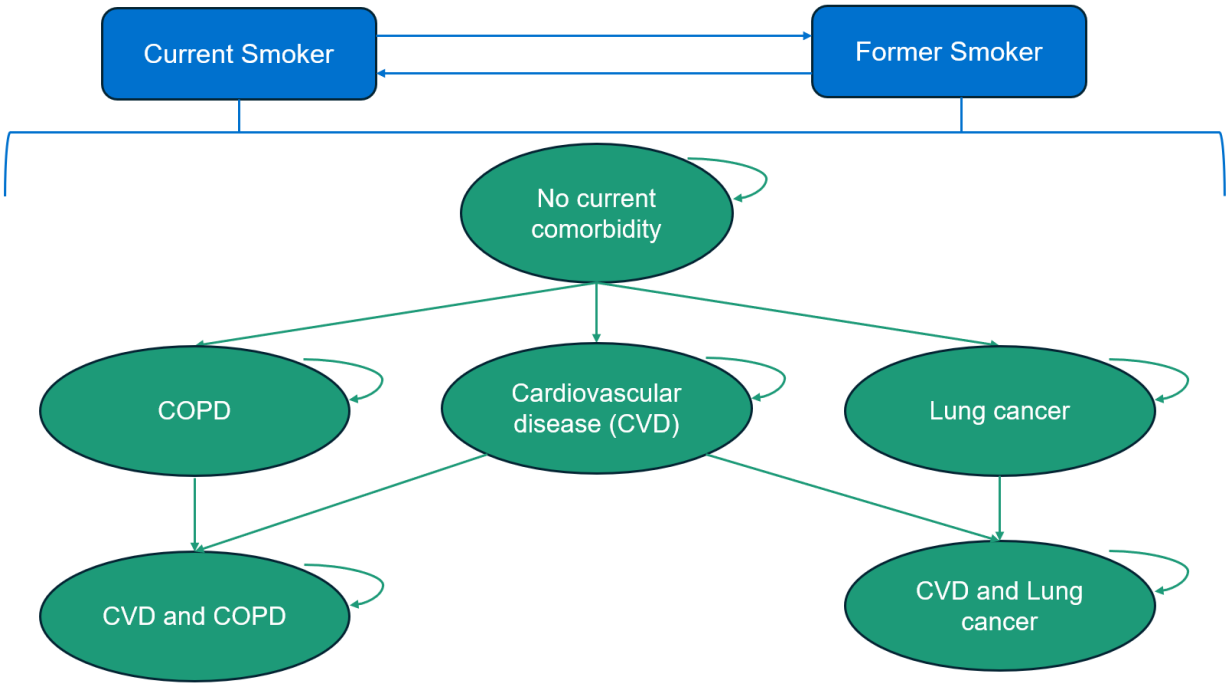
The model simulated the treatment's impact on preventing the occurrence of key smoking-related events (Figure 4.1.). All patients began the model as current smokers who smoked on average about 20 cigarettes per day. Transitions to former smoker status were informed by ICER's internal network meta-analysis, with the same probability of relapse back to current smoking informed by literature, regardless of smoking-cessation strategy. The model focused on smoking-related chronic conditions, specifically cardiovascular disease (CVD) events, chronic obstructive pulmonary disease, and lung cancer. Transition probabilities to these events were dependent on smoking status, reflecting differential risks for current versus former smokers as seen in observational studies. Patients remained in the model until they died. All patients transitioned to death from the alive health states. Additional details regarding mortality can be found in Section 4.5.

Our model leveraged prior models used to assess smoking cessation, including the BENESCO model. However, our model diverged in several clinically motivated ways. First, asthma was not included as a separate health state. While smoking is a known trigger for asthma exacerbations, especially in younger populations, asthma generally contributes less to long-term morbidity and cost compared to COPD, lung cancer, or CVD events across a population of adult smokers. Second, we consolidated myocardial infarction and stroke into a single composite CVD event health state and used literature estimates that included peripheral vascular disease when available as this was determined to be an important smoking-relating condition. This approach reflects the shared pathophysiology, risk factors, and overlapping treatment pathways for major atherosclerotic events. Third, although the BENESCO model included a distinct health state for recurrent CVD events, we captured the clinical and economic impact of these events with one health state by applying literature-based probabilities for recurrence and event-specific cost estimates that vary by acute and post-CVD

events to capture the elevated burden of recurrent cardiovascular disease (CVD) events. This approach is anticipated to balance model simplicity with the need to reflect long-term clinical and economic consequences of chronic CVD morbidity.

Changes from the revised Evidence Report to the Final Evidence Report: No changes were made to the economic evaluation between the Draft Evidence Report and the revised Evidence Report.

Figure 4.1. Model Schematic



COPD: chronic obstructive pulmonary disease; CVD: cardiovascular disease

Note: Acute CVD event costs and health impacts are captured as patients transition into a CVD health state

4.2. Key Model Choices and Assumptions

Our model includes several assumptions stated below.

Table 4.1. Key Model Assumptions

Assumption	Rationale
All former smokers shared the same transition probabilities for experiencing a CVD event or developing COPD or lung cancer, regardless of time since smoking cessation	Due to the memoryless nature of Markov models, we did not stratify former smokers by time since quitting. We acknowledge this is a simplification as the risk declines with time. This is consistent with published economic models, which report risk estimates dichotomized as current vs. former smokers without further granularity.
All former smokers had the same probability of relapse to current smoking, regardless of time since smoking cessation and smoking cessation strategy	Like the above, the Markov structure requires consistent transition probabilities between cycles. While relapse risk is known to decline over time, available data and models typically treat relapse as a constant probability due to lack of robust longitudinal data on relapse rates stratified by cessation duration.
Patients who develop COPD cannot develop lung cancer and vice versa	This simplification reduces model complexity and avoids health state proliferation, which would require data on joint disease incidence for transition probabilities and interactions affecting health state costs, quality of life, mortality, and other outcomes that are not readily available.
COPD and lung cancer each were modelled as a single health state with an average utility value, rather than stratifying by severity	This simplification aligns with the goal of capturing long-term health impacts without modeling detailed disease progression. Averaging across the severity spectrum allows each condition's overall burden to be captured while maintaining model parsimony.
Utility values for comorbid conditions were combined multiplicatively using age-adjusted baseline utilities	This approach prevents overestimation of disutility when multiple conditions are present and reflects standard practice in economic modeling. Multiplicative combination is recommended when empirical data on joint health state utilities are unavailable, and age adjustment allows more realistic baseline utility values over time.
Health state costs for smoking-related conditions were estimated additively	Consistent with ICER and prior modeling efforts, we assume additive costs across health states, recognizing this provides a conservative estimate in the absence of robust interaction data.

CVD: cardiovascular disease, COPD: chronic obstructive pulmonary disease, US: United States

4.3. Populations

The population of focus for the economic evaluation was based on patients from the ORCA-2 and ORCA-3 trials, which assessed 12 weeks of treatment with cytisinicline for smoking cessation compared to placebo. Baseline characteristics in Table 4.2. were calculated as a weighted average across both clinical trials.

Table 4.2. Baseline Population Characteristics

Characteristics	Value (Weighted Average)
Mean Age (SD)	52.0 (11.8) years
Percent Male	44.6%
Daily Average Cigarettes Smoked (SD)	19.7 (7.4)
Source	ORCA-2 & ORCA-3[11,12]

SD: standard deviation

4.4. Interventions and Comparators

Interventions

The list of interventions was developed with input from patient organizations, clinicians, manufacturers, and payers on which treatments to include. The full list of interventions is as follows:

- 12 weeks of cytisinicline with behavioral support

Comparators

The comparators for this intervention were:

- 12 weeks of varenicline with behavioral support
- Behavioral support alone

4.5. Input Parameters

Clinical Inputs

Key clinical inputs to the model included transition probabilities, mortality, and treatment effects on smoking cessation. Transition probabilities were derived from ICER's NMA and existing literature. Mortality inputs were also informed by published literature.

Transition Probabilities

We used estimates from studies that assessed the incidence of smoking-related conditions (COPD, lung cancer, and CVD events) in current and former smokers (Table 4.3). For the elevated risk of a CVD event among patients with COPD and lung cancer, we applied hazard ratio estimates from the literature (Table 4.4). For these clinical inputs, additional details regarding the studies that were used can be found in Supplemental Section E2.

Table 4.3. Transition Probabilities Per Cycle (3 Months)

Parameter	Current Smoker	Former Smoker	Source
COPD	0.31%-0.62% (age specific)	0.10%-0.31% (age specific)	Terzikhan et al. 2016[28]
Lung Cancer	0.05%	0.04%	Tindle et al. 2018[29]
CVD Event	0.31%	0.29%	McEvoy et al. 2015[30]

COPD: chronic obstructive pulmonary disease, CVD: cardiovascular disease

Table 4.4. Hazard Ratios for a CVD Event

Parameter	Hazard Ratio (Relative to Patients Without COPD or Lung Cancer)	Source
CVD Event with COPD	Acute MI: 1.22-1.78 (age specific) Acute stroke: 1.06-2.21 (age specific)	Feary et al. 2010[31]
CVD Event with Lung Cancer	2.33	Zhang et al. 2024[32]

COPD: chronic obstructive pulmonary disease, CVD: cardiovascular disease, MI: myocardial infarction

Treatment Effects on Smoking Cessation

The treatment effects of cytisinicline and varenicline on smoking cessation (i.e., movement from current smoker to former smoker) were estimated from ICER's NMA. The abstinence rate of 12.2% for behavior therapy alone over 16 weeks from the NMA was converted to a probability of 10.06% for our three-month cycle. Relative treatment effects for cytisinicline and varenicline from the random-effects NMA were then applied to the three-month smoking cessation probability for behavioral therapy alone. Treatment effects for all smoking cessation strategies were only applied to the first cycle of the model when the full course of treatment was expected to be completed (Table 4.5).

Table 4.5. Relative Risk Estimates for Smoking Cessation from Weeks 9 to Week 24 of Cytisinicline and Varenicline Compared to Behavior Therapy Alone

Intervention	Relative Risk	Source
Cytisinicline	2.71 (95% CrI: 1.91, 4.02)	ICER internal network meta-analysis
Varenicline	2.45 (95% CrI: 2.19, 2.71)	

CrI: credible interval

Relapse from Former Smoking to Current Smoking

It is well established that relapse risk declines as time since last cigarette increases. Because our model does not track time since quit, we used a single, time-invariant relapse probability. We approximated this relapse input from a UK study where the cumulative relapse risk in the short-term after quitting (<5 years since quit) was 42.5%.[33] Assuming a constant annual risk over this interval, the annual relapse probability was 12.9%, which was then converted to our model's three-month cycle and estimated to be 3.35%. The same annual estimate was used by a prior health technology assessment of cytisinicline versus varenicline.[34] Since relapse probability is known to decrease with longer cessation times, we ran a scenario analysis using a 1.00% three-month cycle relapse probability (based on those >=5 years since quit from the Hawkins et al. study) starting in year five of the model.

Mortality

We detail our approach to estimating mortality due to specific conditions and by smoking status in Supplemental Section E2. In short, we derived a never-smoker baseline by starting from the 2023 US life table, converting age-specific death probabilities to hazards, dividing by a mixture factor built from contemporary smoking prevalence and all-cause relative risks for current and former smokers, converting back to probabilities, and then applying condition-specific relative risks to obtain disease-specific mortality (Table 4.6).

Table 4.6. Mortality Inputs[35]

Parameter	Relative Risk (Current Smoker vs. Never Smoked)	Relative Risk (Former Smoker vs. Never Smoked)
All-Cause	2.76	1.47
COPD	22.35	8.09
Lung Cancer	25.66	6.70
CVD Event*	2.59	1.33

COPD: chronic obstructive pulmonary disease, CVD: cardiovascular disease

*The relative risk for a cardiovascular disease event was estimated from ischemic heart disease and stroke

Adverse Events

Consistent with previously published models and cost-effectiveness analyses of smoking cessation therapies, adverse events (AEs) were not explicitly included in the model.[27,36-38] While both cytisinicline and varenicline are associated with AEs, most commonly nausea, headache, insomnia, and abnormal dreams, these events are generally mild to moderate and self-limiting.[11,12,39] While these AEs may temporarily affect health-related quality of life, there is limited evidence that they lead to the use of additional health care resources, which limits their relevance for economic modeling purposes. Furthermore, serious AEs were reported in the clinical trials as composite

outcomes, without sufficient detail to assign condition-specific costs or disutilities. Given these limitations, and in line with prior analyses, we excluded direct modeling of AEs.

Health State Utilities

Health state utilities were derived from publicly available literature and applied to relevant health states in the model (Table 4.7). Age-specific background utility values for the general US population were sourced from a nationally representative EQ-5D-5L valuation study, which conducted face-to-face interviews across six metropolitan areas selected for their demographic representativeness.[40] Utilities were calculated using the US-specific EQ-5D-5L value set and served as baseline age-adjusted utility inputs.

Utilities for COPD and lung cancer were obtained from the literature. Although both conditions have distinct severity stages, our model captured each condition as a single health state. Rather than modeling disease progression, we applied an average utility value that reflects the full spectrum of severity for each condition. This simplification aligns with the model's purpose and available data, as stratifying utility inputs by disease stage would require longitudinal data that are not readily available and is beyond the intended scope of this analysis. For health states with multiple smoking-related outcomes (e.g. lung cancer with CVD event), utilities were combined multiplicatively, consistent with prior approaches from the literature.[41] This approach assumes that each additional chronic condition reduces remaining quality of life proportionally rather than absolutely. To estimate utility multipliers, we obtained utility decrements for individuals with the condition.[42] These values were used to derive multipliers under the assumption that the baseline utility for a healthy individual without the condition is approximately 0.851.[40] For example, the disutility associated with a stroke is -0.0524, which would equate to a multiplier of (0.851-0.0524)/0.851=0.94.

In addition, a disutility of −0.035 was applied to current smokers to reflect the impact of smoking on health-related quality of life based on a prior analysis of approximately 13,000 survey respondents from England. The study found that the utility difference between heavy and former smokers was associated with greater reported problems in anxiety/depression, mobility, and pain/discomfort.[43]

Table 4.7. Health State Utilities

Parameter	Value	Source
Baseline Utility	Age-specific	Jiang R et al. 2021[40]
COPD	0.79*	Rutten-van Moken et al. 2006 [44]
Lung Cancer	0.78†	Tramontano AC et al. 2015 [45]
Utility Multiplier: Post CVD Event	0.94‡	Sullivan P et al. 2006[42]
Disutility: Acute CVD Event (One Cycle)	-0.17‡	Matza et al. 2015[46]
Disutility: Smoking	-0.035	Vogl M et al. 2012[43]

COPD: chronic obstructive pulmonary disease, CVD: cardiovascular disease

*Calculated average across GOLD stage 2 through 4

†Calculated average across stage 1 through 4

‡Calculated average of myocardial infarction and stroke

Caregiver Disutilities

Details on the caregiver disutilities used in the scenario analysis for the modified societal perspective are detailed in the Supplemental Section E2.

Drug Utilization

Details on the drug utilization inputs are provided in the Supplemental Section E2.

Cost Inputs

All costs used in the model were updated to 2024 dollars using the medical consumer price index.[47]

Drug Costs

With an FDA PDUFA date of June 20, 2026, the price of cytisinicline is currently not known. We used a placeholder price of $5,000 for the 12-week treatment course based on estimates from IPD Analytics (Table 4.8). For varenicline, we used the median price of all generic options for varenicline from Redbook.

Table 4.8. Drug Costs

Drug	WAC per mg	Discount from WAC	Net Price per Dose	Net Price per Course of Treatment
Cytisinicline	$6.61*	Not Applicable*	$6.61*	$5,000*
Varenicline (Generic)	$4.17†	Not Applicable†	$4.17†	$664†

WAC: wholesale acquisition cost

*Placeholder price

†Represents the median price of all available generic options

Non-Drug Costs

Non-drug health care costs included both related and unrelated components to smoking-related conditions in the model (Table 4.9). Related health care costs attributable to each smoking-related outcome were obtained from the literature. An additive approach was used to estimate costs for health states involving multiple outcomes, consistent with prior cost-effectiveness studies. In addition, related health care costs for a CVD event, taken as the average for myocardial infarction (MI) and stroke, were applied additively to other costs for patients who experience these events. Details regarding the studies used to estimate non-drug costs are in Supplemental Section E2.

Table 4.9. Health State Costs Per Cycle (Three Months)

Input	Value	Source
No Comorbidity	$1,798-$4,046 (age-specific)	Jiao & Basu 2021[48]
Acute CVD Event (One Time Cost)	$29,984	Tajeu 2024[49]
Post CVD Event	$1,861	Bishu 2020, Girotra 2020[50,51]
Post CVD Event Unrelated	$3,566-$4,932 (age-specific)	Jiao & Basu 2021[48]
COPD Related	$2,455	Wallace AE et al. 2019[52]
COPD Unrelated	$4,528	
Lung Cancer Related	$14,549	Apple J et al. 2023[53]
Lung Cancer Unrelated	$8,025	

COPD: chronic obstructive pulmonary disease, CVD: cardiovascular disease

Direct Non-Medical Costs

From the modified societal perspective, we estimated the direct non-medical cost savings associated with smoking cessation. Specifically, we assumed an average retail price of $9.83 per pack of cigarettes in the US.[54] Following the recommendations of the Second Panel on Cost-Effectiveness in Health and Medicine, we excluded excise taxes by subtracting the average per-pack tax of $2.51.[54] The resulting net cost was applied to the estimated number of years smoked per treatment arm, assuming patients would have smoked one pack per day, consistent with baseline characteristics in cytisinicline's clinical trials.

4.6. Model Outcomes

Model outcomes included total life years (LYs) gained, quality-adjusted life years (QALYs) gained, equal-value life years (evLYs) gained, and total costs for each intervention over a lifetime time horizon. Details regarding how the evLY is calculated are provided in the Supplemental Materials. The model outcomes also included total number of smoke-free years, lung cancer cases, COPD cases, and CVD events. Costs, LYs, QALYs, and evLYs gained were also reported by the health state to understand the contribution of different costs elements. Total costs, LYs, QALYs, and evLYs gained were reported as discounted values, using a discount rate of 3% per annum. A full description of the evLY calculation can be found in the Supplemental Section E1.

4.7. Model Analysis

Cost-effectiveness was estimated using the incremental cost-effectiveness ratios, with incremental analyses comparing cytisinicline with behavioral support to varenicline with behavioral support or behavioral support alone. The base-case analysis took a health care system perspective (i.e., focus on direct medical care costs only).

4.8. Results

Base Case Results

The total discounted costs, QALYs, evLYs, and LYs are detailed in Table 4.10 for the three treatment arms. Over a lifetime horizon at the placeholder price of $5,000 for a 12-week treatment course, treatment with cytisinicline with behavioral support resulted in higher incremental costs of $4,400 and incremental gains in QALYs and evLYs of approximately 0.01 and 0.02, respectively, compared to varenicline with behavioral support. Compared to behavior support alone, cytisinicline with behavioral support had higher incremental costs of $5,500 and incremental gains in QALYs and evLYs of 0.08 and 0.09, respectively. Additionally, cytisinicline with behavioral support led to one and three fewer COPD cases per 1,000 individuals compared to varenicline with behavioral support and behavioral support alone, respectively. Other clinical outcomes assessed are detailed in the Supplemental Section E3.

Table 4.10. Results for the Base Case for Cytisinicline with Behavioral Support Compared to Varenicline with Behavioral Support and Behavioral Support Alone

Treatment	Intervention Acquisition Costs*	Total Costs*	COPD Cases†	QALYs	evLYs	Life Years
Cytisinicline + Behavioral Support	$5200	$195,000	168	10.72	10.72	13.97
Varenicline + Behavior Support	$880	$190,000	168	10.71	10.71	13.96
Behavioral Support Alone	$200	$189,000	172	10.63	10.63	13.89

COPD: chronic obstructive pulmonary disease, evLYs: equal value of life years gained, QALYs: quality-adjusted life years

*Based on placeholder price

†Per 1,000 individuals

Table 4.11 presents the incremental cost-effectiveness ratios for the base case analysis, which includes estimates for the incremental cost per QALY gained, incremental cost per evLY gained, and incremental cost per LY gained. For cytisinicline with behavioral support compared to varenicline with behavioral support, the incremental cost per QALY gained was approximately $339,000 and the incremental cost per evLY gained was approximately $317,000 from the health care sector perspective. For cytisinicline with behavioral support compared to behavioral support alone, the incremental cost per QALY gained was approximately $64,400 and the incremental cost per evLY gained was approximately $60,200 from the health care sector perspective.

Table 4.11. Incremental Cost-Effectiveness Ratios for the Base Case

Treatment	Comparator	Cost per QALY Gained*	Cost per evLY Gained*	Cost per Life Year Gained*
Cytisinicline + Behavioral Support	Varenicline + Behavior Support	$339,000	$317,000	$352,000
Cytisinicline + Behavioral Support	Behavioral Support Alone	$64,400	$60,200	$66,800

evLYs: equal value of life years gained, QALY: quality-adjusted life year

*Based on placeholder price

Sensitivity Analyses

Results from one-way sensitivity analyses and probabilistic sensitivity analyses can be found in Supplemental Section E4.

Scenario Analyses

We conducted numerous scenario analyses to examine uncertainty and potential variation in the findings. A list of these scenarios and the results can be found in Supplemental Section E5.

Threshold Analyses

Threshold analyses were conducted to calculate the treatment course cost needed to meet commonly accepted cost-effectiveness thresholds for QALY gained (Table 4.12) and evLY gained (Table 4.13).

Table 4.12. QALY-Based Threshold Analysis Results

Treatment	Comparator	Treatment Course Cost*	Treatment Course Cost to Achieve $50,000 per QALY Gained	Treatment Course Cost to Achieve $100,000 per QALY Gained	Treatment Course Cost to Achieve $150,000 per QALY Gained	Treatment Course Cost to Achieve $200,000 per QALY Gained
Cytisinicline + Behavioral Support	Varenicline + Behavioral Support	$5,000	$1,200	$1,900	$2,500	$3,200
Cytisinicline + Behavioral Support	Behavioral Support Alone	$5,000	$3,800	$8,000	$12,300	$16,600

QALY: quality-adjusted life year , WAC: wholesale acquisition cost

*Placeholder price for a 12-week treatment course

Table 4.13. evLY-Based Threshold Analysis Results

Treatment	Comparator	Treatment Course Cost*	Treatment Course Cost to Achieve $50,000 per evLY Gained	Treatment Course Cost to Achieve $100,000 per evLY Gained	Treatment Course Cost to Achieve $150,000 per evLY Gained	Treatment Course Cost to Achieve $200,000 per evLY Gained
Cytisinicline + Behavioral Support	Varenicline + Behavioral Support	$5,000	$1,300	$2,000	$2,700	$3,400
Cytisinicline + Behavioral Support	Behavioral Support Alone	$5,000	$4,100	$8,600	$13,200	$17,800

evLYs: equal value of life years gained, WAC: wholesale acquisition cost

*Placeholder price for a 12-week treatment course

Model Validation

Details on our model validation process and comparison to prior economic models can be found in Supplemental Section E6.

Uncertainty and Controversies

There were limitations and uncertainties that affected our model results. First, we limited the health consequences of smoking to COPD, lung cancer, and CVD because these outcomes are the primary drivers of the morbidity and mortality seen in prior models and have the most publicly available evidence. This choice omitted other smoking harms (e.g., other cancers) so our estimates may be conservative if quitting also reduced health risks we did not model. We also used a

simplified modeling framework (mutually exclusive COPD and lung cancer states with elevated CVD added) to control the number of modeled health states. This structural simplification likely underestimated incremental clinical outcomes and overestimated incremental costs of cytisinicline relative to behavioral therapy alone since it omits the elevated lung cancer risk among individuals with COPD and therefore underestimated downstream health and cost offsets based on literature.[55] This concern is specific to this comparison (i.e., cytisinicline vs. behavioral therapy alone) where we observed a small difference in COPD cases. We do not anticipate a similar impact in the comparison of cytisinicline versus varenicline as we did not see a difference in the number of COPD cases. Additionally, limited evidence on joint disease states required assumptions about how risks were combined when conditions coexist.

Other uncertainties included an assumed single quit attempt at treatment initiation even though most smokers attempt quitting multiple times, and we applied a constant relapse probability per cycle rather than allowing relapse risk to decline with time since quit. Additionally, we assumed full adherence to all smoking cessation interventions for costing purposes, while trial-based treatment effects include nonadherent patients. These choices reflect data availability and alignment with earlier models but may overestimate relapse long-term.

To model mortality, we used contemporary relative risks from a recent study and a revised never-smoker life table. Compared with previous models that estimated mortality risks from older data, our inputs implied higher excess mortality for smoking-related diseases, which likely increased the incremental LYs and QALYs projected for more effective cessation therapies.

Finally, cost inputs introduced additional uncertainty. We used US cost data where available, but some epidemiologic and resource estimates come from non-US sources. Importantly, the price of cytisinicline is currently not known. Our placeholder price ($5,000 per 12-week treatment course) is uncertain and some analysts have suggested a lower estimated price. Additionally, when we used the lowest price for generic varenicline from Redbook in a scenario analysis instead of the median price in the base case ($25 vs. $664, respectively), the incremental cost-effectiveness ratios for cost per QALY and evLY gained in the comparison of cytisinicline versus varenicline became higher.

We focused the economic model on adults trying to quit cigarettes with the three interventions most relevant to our policy question (behavior support alone, cytisinicline, and varenicline). We did not model vaping cessation or additional comparators including NRT products because the clinical review found limited data. Furthermore, the use of cytisinicline for vaping was not included in the economic model due to insufficient evidence.

4.9. Summary and Comment

In our lifetime model, smokers who experienced one quit attempt with cytisinicline and behavioral support resulted in small gains in LYs, QALYs, and evLYs compared to varenicline and behavioral support or behavioral support alone. Compared to behavioral support alone, cytisinicline and behavioral support is estimated to be cost-effective at commonly accepted thresholds. Compared to varenicline and behavioral support, based on its current placeholder price, cytisinicline and behavioral support exceeds commonly accepted thresholds and would require sizeable price reductions to be considered cost-effective. The cost-effectiveness of cytisinicline will depend on its price and the smoking cessation intervention it is compared to.

5. Benefits Beyond Health and Special Ethical Priorities

Our reviews seek to provide information on benefits beyond health and special ethical priorities offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that are not available in the evidence base nor could be adequately estimated within the cost-effectiveness model. These elements are listed in the table below, with related information gathered from patients and other stakeholders. Following the public deliberation on this report the appraisal committee will vote on the degree to which each of these factors should affect overall judgments of long-term value for money of the intervention in this review.

Table 5.1. Benefits Beyond Health and Special Ethical Priorities

Benefits Beyond Health and Special Ethical Priorities	Relevant Information
There is substantial unmet need despite currently available treatments.	There are still many individuals who smoke despite currently available therapies and smoking has significant short and long-term health consequences. To inform unmet need as a benefit beyond health, the results for the evLY and QALY absolute and proportional shortfalls have been reported below. evLY shortfalls: • Absolute shortfall: 11.04 • Proportional shortfall: 43.64% QALY shortfalls: • Absolute shortfall: 10.01 • Proportional shortfall: 41.25% The absolute and proportional shortfalls represent the total and proportional health units of remaining quality adjusted life expectancy, respectively, that would be lost due to un- or under-treated illness. For this analysis, untreated or under-treated illness is represented by behavioral therapy alone. Similar shortfalls were found when untreated or undertreated illness was represented by varenicline (i.e., <0.5% and <0.2 proportional and absolute shortfall differences, respectively, compared to the findings reported above using behavioral therapy alone). Please refer to the ICER Reference Case – Section 2. Quantifying Unmet Need (QALY and evLY Shortfalls) for the shortfalls of other conditions assessed in prior ICER reviews.

Benefits Beyond Health and Special Ethical Priorities	Relevant Information
This condition is of substantial relevance for people from a racial/ethnic group that have not been equitably served by the health care system.	People living with serious psychiatric illness and those with low socioeconomic status are overrepresented in the population of current smokers in the United States. ICER calculated the Health Improvement Distribution Index, looking at the relative proportion of any health gains from smoking cessation for the following groups with a higher prevalence of cigarette smoking than the general US population (see Supplement A1): Non-Hispanic American Indian or Alaska Native = 1.4 Smoking rates are also high in the Native Hawaiian/Pacific Islander population.
The treatment is likely to produce substantial improvement in caregivers' quality of life and/or ability to pursue their own education, work, and family life.	The treatment is not expected to substantially affect caregivers' quality of life.
The treatment offers a substantial opportunity to improve access to effective treatment by means of its mechanism of action or method of delivery.	Since other oral therapies for smoking cessation are available, this treatment does not provide improved access through its delivery method or mechanism of action.
Other	Because cytisinicline is derived from the seeds of an acacia plant, it can be marketed as a "natural" medicine, which may increase acceptability and thus uptake among a subset of people who smoke.

Midwest CEPAC

At the public meeting, the Midwest CEPAC deliberated and voted on the relevance of specific potential other benefits and contextual considerations on judgments of value for the interventions under review. The results of the voting are shown below. Further details on the intent of these votes to help provide a comprehensive view on long-term value for money are provided in the ICER Value Assessment Framework.

To help inform judgments of overall long-term value for money, please indicate your level of agreement with the following statements:

Table 5.2. Midwest CEPAC Votes on Benefits Beyond Health and Special Ethical Priorities - Condition

Benefits Beyond Health and Special Ethical Priorities	Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree
There is substantial unmet need despite currently available treatments	0	0	0	6	8
This condition is of substantial relevance for people from a health/ethnic group that have not been equitably served by the health care system.	0	0	5	6	3

A majority of the council voted that there is substantial unmet need despite currently available treatments.

A majority of the council voted that this condition is of substantial relevance for people from a racial/ethnic group that has not been equitably served by the health care system.

To reach this conclusion, participants discussed disparities in smoking prevalence and access to cessation resources. One council member emphasized the strong correlation between race/ethnicity, income, and insurance coverage, and considered this context in his vote. Another member highlighted high rates of menthol cigarette use in the Black population and noted the historical targeting of menthol products toward certain racial/ethnic groups.

To help inform judgments of overall long-term value for money, please indicate your level of agreement with the following statements based on the relative effects of cytisinicline versus varenicline:

Table 5.3. Midwest CEPAC Votes on Benefits Beyond Health and Special Ethical Priorities - Treatment

Benefits Beyond Health and Special Ethical Priorities	Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree
The treatment is likely to produce substantial improvement in caregivers' quality of life and/or ability to pursue their own education, work, and family life	2	3	6	2	1
The treatment offers a substantial opportunity to improve access to effective treatment by means of its mechanism of action or method of delivery	6	7	1	0	0
Other: The treatment may increase acceptability and thus uptake among a subset of people who smoke because cytisinicline is derived from the seeds of an acacia plant and can be marketed as a 'natural medicine'.	0	1	12	1	0

A majority of the council remained 'neutral' on whether cytisinicline is likely to produce substantial improvement in caregiver quality of life and/or ability to pursue their own education, work, and family life.

One council member shared he voted 'strongly disagree,' because available evidence does not show a substantial difference in quit rates between the two treatments, so he finds it unlikely that there would be downstream differences in caregiver outcomes. Another member focused on the quality-of-life benefits associated with smoking cessation more broadly, such as reduced exposure to secondhand smoke; he rationalized that these benefits would not depend on whether cytisinicline or varenicline was used, but rather on treatment versus no treatment.

A majority of the council voted that cytisinicline does not offer a substantial opportunity to improve access to treatment by means of its mechanism of action or method of delivery. It was noted that both cytisinicline and varenicline have similar methods of delivery as oral medications. One council member suggested that despite these similarities, some patients may be more willing to try cytisinicline due to negative publicity surrounding varenicline.

A large majority of the council remained 'neutral' on whether the treatment may increase acceptability and uptake among a subset of people who smoke because cytisinicline is derived from the seeds of an acacia plant, and can be marketed as ‘natural' medicine.

Many council members raised concerns about framing this medication as 'natural,' noting that the term lacks scientific clarity and does not inherently imply safety. At the same time, one member acknowledged that patients might find the 'natural' label more appealing, which contributed to his 'neutral' vote. This discussion highlighted the challenge of balancing patient appeal with scientific clarity.

6. Health Benefit Price Benchmark

The threshold prices for cytisinicline with behavioral support from the health care sector perspective, based on both evLYs and QALYs gained, are presented in Table 6.1 below. The Health Benefit Price Benchmark (HBPB) for a drug is defined as the price range that would achieve incremental cost-effectiveness ratios between $100,000 per QALY and $150,000 per evLY gained. The HBPB for cytisinicline is $1,900 to $2,700.

Table 6.1. Annual Cost-Effectiveness Threshold Prices for Cytisinicline with Behavioral Support

Annual Prices Using…	Annual WAC	Annual Price at $100,000 Threshold	Annual Price at $150,000 Threshold	Discount from WAC* to Reach Threshold Prices
Cytisinicline with Behavioral Support vs. Varenicline with Behavioral Support				
QALYs Gained	$5,000*	$1,900	$2,500	49% - 62%
evLYs Gained	$5,000*	$2,000	$2,700	46% - 60%

evLY: equal value life year, QALY: quality-adjusted life year, WAC: wholesale acquisition cost

*Placeholder price for a 12-week treatment course

Midwest CEPAC Votes

Long-term value for money votes were not taken at the public meeting because a net price for cytisinicline was not available.

7. Potential Budget Impact

7.1. Overview of Key Assumptions

Results from the cost-effectiveness model were used to estimate the total potential budgetary impact of cytisinicline with behavioral support for adults who are interested in quitting cigarettes. Potential budget impact is defined as the total differential cost of using the new therapy rather than relevant existing therapy for the treated population, calculated as differential health care costs (including drug costs) minus any offsets in these costs from averted health care events. All costs were undiscounted and estimated over a five-year time horizon. We used the placeholder price of $5,000 per 12-week treatment course and the threshold prices (at $50,000, $100,000, $150,000, and $200,000 per evLY) for cytisinicline in our estimate of potential budget impact.

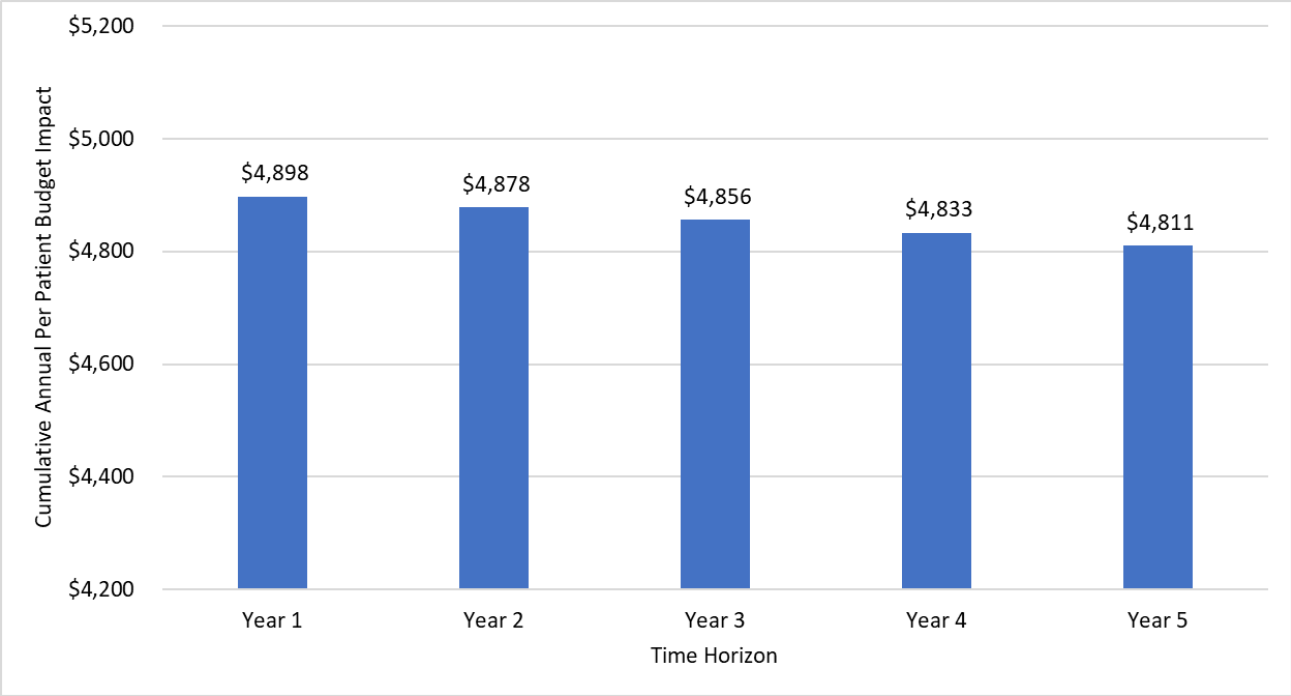
This budget impact analysis included the estimated number of individuals in the US who would be eligible for cytisinicline. To estimate the size of the potential candidate population, we used inputs for the percentage of adults who smoke cigarettes (11.6%) and the percentage of adults who are interested in quitting (67.7%).[6] Applying these sources to the total US population of adults averaged over the next five years (270,906,499) results in estimates of 21,274,829 eligible patients in the US.%).[6,56] For the purposes of this analysis, we assume that 20% of these patients would initiate treatment in each of the five years, or 4,254,965 patients per year. At baseline, we assume 10% of the eligible population are being treated with varenicline with behavioral support, and 90% are being treated with behavioral support alone.[57]

7.2. Results

Figure 7.1 illustrates the cumulative annual per patient treated population budget impact for cytisinicline with behavioral support compared to a baseline of patients split evenly between varenicline with behavioral support and behavioral support alone. The cumulative per patient budget impact represents the incremental costs of cytisinicline compared to the baseline per patient across all patients treated within a time horizon (including those who initiated cytisinicline in previous years), assuming cytisinicline is used with 20% uptake each year over five years.

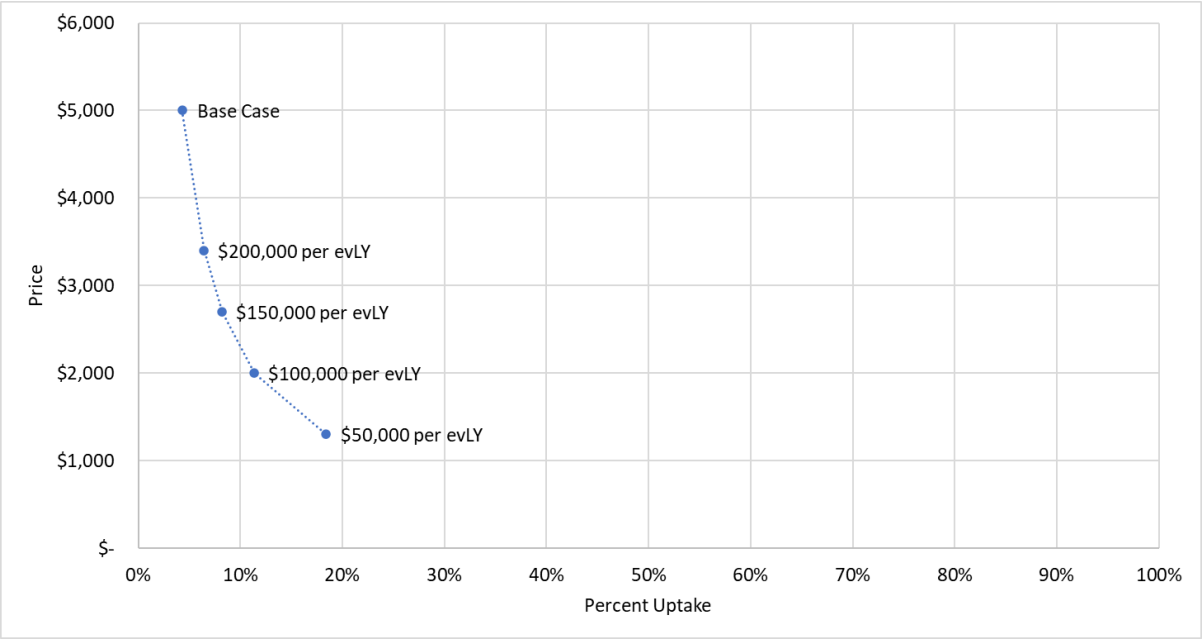
At cytisinicline's placeholder price of $5,000 per 12-week treatment course, the average annual budget impact per patient was $4,898 in the first year, and decreased to $4,811 by year five. The average annual budget impact decreases slightly throughout the five year time horizon despite the treatment course being limited to year one due to the small changes in costs from averted health care events.

Figure 7.1. Cumulative Annual Per Patient Budget Impact of Cytisinicline with Behavioral Support Compared to Varenicline with Behavioral Support and Behavioral Support Alone at a Placeholder Price



Results showed that 4.3% of eligible patients could be treated with cytisinicline with behavioral support at the placeholder price of $5,000 per 12-week treatment course before reaching the potential budget impact threshold of $880 million per year. At the $50,000, $100,000, $150,000 and $200,000 per evLY threshold prices for cytisinicline compared to varenicline with behavioral support, ($1,300, $2,000, $2,700, and $3,400), 18.4%, 11.4%, 8.1%, and 6.4% of patients could be treated before reaching the potential budget impact threshold (Figure 7.2).

Figure 7.2. Percentage of Eligible Patients Treated Without Reaching the Potential Budget Impact Threshold at Placeholder and Threshold Prices for Cytisinicline with Behavioral Support Compared to Varenicline with Behavioral Support



evLY: equal value of life years

At the $50,000, $100,000, $150,000 and $200,000 per evLY threshold prices for cytisinicline compared to behavioral support alone, ($4,100, $8,600, $13,200, and $17,800), 5.3%, 2.5%, 1.6%, and 1.2% of patients could be treated before reaching the potential budget impact threshold (Supplement Figure F1.1).

Access and Affordability Alert

The goal of the Access and Affordability alert is to signal that the additional health care costs introduced by a new intervention may be difficult for the health care system to absorb over the short term. In this situation, other needed services may be displaced, or health care insurance costs may rapidly rise, which would threaten sustainable access to high-value care for all patients.

At a placeholder price of $5,000 per treatment course, and estimated eligibility and uptake assumptions, approximately 4% of patients expected to be eligible for treatment over five years could receive therapy without exceeding the potential budget impact threshold of $880 million per year. At the lower end of ICER's threshold prices for cytisinicline ($1,300 per treatment course at $50,000 per evLY), approximately 18% of patients could be treated. Given the uncertainty in the actual price of cytisinicline and anticipated uptake, ICER is not issuing an access and affordability alert for cytisinicline.

8. Policy Recommendations

Following the Midwest CEPAC's deliberation on the evidence, a policy roundtable discussion was moderated by Sarah Emond around how best to apply the evidence on the use of cytisinicline. The policy roundtable members included two patient advocates, two clinical experts, two payers, and one representative from a purchaser or large employer. The discussion reflected multiple perspectives and opinions, and therefore, none of the statements below should be taken as a consensus view held by all participants. The top-line policy implications are presented below, and additional information can be found here.

Health Equity

All Stakeholders

Recommendation 1

All stakeholders have a responsibility and an important role to play in ensuring that an effective new treatment for patients who smoke is introduced in a way that will help reduce health inequities and stigma.

Smoking remains the leading preventable cause of death in the United States. Individuals of lower socioeconomic status and those with serious psychological illness are over-represented among smokers. These two groups already suffer from reduced access to quality healthcare. In addition, smokers face significant stigma and shame. They are reminded of this daily, as they can no longer smoke in workplaces, schools, bars, and restaurants in much of the country. When diagnosed with smoking-related illnesses, many patients' reaction is that they brought this on themselves. Despite nicotine being the most addictive legally available drug, they still blame themselves for a failure of will. And some in the broader community, including physicians, blame them as well.

We can all learn from the work of those engaged with patients who are struggling with obesity. Physicians and advocates have reframed the conception of obesity from personal failure to a complex health and social issue. We have shifted the narrative from moralizing "will power" stories to person-first language, with biological and environmental explanations. Guidelines now stress empathy, asking permission to talk about weight, providing privacy around weigh-ins, and recognizing weight bias as a quality-of-care issue rather than a motivational tool. Similar efforts for smokers offer the opportunity to engage them more deeply in their health care and to support them in their efforts to quit. As noted in the evidence report, seven out of ten smokers want to quit, and more than half try to quit each year.

To address health equity concerns:

Manufacturers should take the following actions:

- **Set the price of cytisinicline immediately to align with the value of added patient benefits.** The price for cytisinicline has not been set, but analyst estimates are as high as $5,000 for a 12-week treatment course, which may lead to significant access limitations. ICER's analysis suggested that treatment would achieve common thresholds for cost-effectiveness if priced between $1,900 to $2,700 for 12 weeks. For context, varenicline (brand name Chantix®) was priced at $250 for a 12-week course at launch and $1,300 just prior to losing patent exclusivity. In addition, the cost for an equivalent 12-week course in Poland would be about $150 dollars. The manufacturer should expect to charge more to account for the process of getting FDA approval, but a more than 30-fold price premium seems excessive.

  Unlike other drugs, the manufacturer was not taking on a high risk of failure to bring cytisinicline to market. Given the extensive clinical trial literature on cytisine elsewhere, the manufacturer could expect success with cytisinicline.

  Furthermore, the Affordable Care Act (ACA) may require that cytisinicline be offered without cost-sharing or prior authorization, as the US Preventive Services Task Force has given smoking cessation with a drug FDA-approved for smoking cessation an A rating. The manufacturer should not misuse this potential advantage in access to patients by setting an excessive price for cytisinicline. The manufacturer should price cytisinicline so that both individual patients and the health system will view the drug as fairly priced, leading to broader access and reducing disparities.

Payers should take the following actions:

- **Ensure that benefit designs developed in conjunction with employers and other plan sponsors do not impose out-of-pocket requirements that create major barriers to appropriate access for vulnerable patients.**

To address concerns about stigma:

Clinicians and Clinical Specialty Societies should take the following actions:

- **Work with patient advocacy organizations to ensure that guidelines and screening protocols on smoking assessment and cessation are patient-centered and sensitive to stigma directed at smokers.**
  Smoking should be referred to as an addiction resulting from biology, targeted marketing, and other social influences. Smoking should never be referred to as a moral failing or a failure of willpower. Patient-centered, empathic language should be used consistently when

talking about people who smoke cigarettes. Shame can drive people away from help and toward covert use or alternative products rather than smoking cessation. Framing cessation as a shared problem solving process—acknowledging addiction, relapse risk, and emotional distress—helps maintain dignity while still clearly conveying the health benefits of quitting.

Payers

Recommendation 1

Payers should use the varenicline coverage policy as a guide for the cytisinicline coverage policy.

There is high certainty evidence that cytisinicline provides substantial net health benefits compared with behavioral therapy alone. Both cytisinicline and varenicline have the same mechanism of action. Indirect evidence supports likely equivalent efficacy with the potential for fewer side effects (nausea) with cytisinicline. There is more than 50 years of clinical experience with cytisinicline for smoking cessation in some European countries, which offers strong support for its efficacy and safety. Finally, the ACA requires that all FDA-approved drugs for smoking cessation be covered for patients because the USPSTF gives them an A rating.

Recommendation 2

Payers should cover telehealth for smoking cessation counseling and smoking cessation drug prescribing.

During the COVID pandemic, telehealth proved its efficacy in mental health care including counseling, psychiatric prescribing, and management of opioid use disorders. Telephone quit lines are readily available in most states and have a proven track record in providing behavioral support for smoking cessation. Adding telehealth as an option for prescribing smoking cessation medications will reduce barriers and increase access to these essential medications and may be particularly helpful in reaching younger patient populations. Additional tools, including text messaging programs and smart phone apps can also support patients in smoking cessation.

Coverage Criteria: General

ICER has previously described general criteria for fair coverage policies that should be considered as cornerstones of any drug coverage policy: https://icer.org/wp-content/uploads/2020/11/Cornerstones-of-Fair-Drug-Coverage--September-28-2020.pdf

Purchasers

Recommendation 1

Purchasers should do more to promote smoking cessation among their covered lives.

Smoking cessation services are underutilized. Purchasers spend a tiny proportion of their pharmaceutical budget on smoking cessation, despite the large expenses due to smoking-related diseases. Greater promotion of smoking cessation services and drugs would be high yield with modest associated expenses.

Patient Advocacy Organizations

Recommendation 1

Patient advocacy organizations should promote peer support.

Peer support can play a significant role in smoking cessation by providing encouragement, shared experiences, practical advice, and accountability, which can improve the likelihood of quitting successfully. People who participate in peer support groups or engage with others who are also trying to quit smoking often feel less isolated and more motivated, which can help them manage cravings and setbacks. Patient advocacy organizations should continue to provide and promote peer support to enhance the success of smoking cessation efforts.

Researchers/Regulators

Recommendation 1

Pharmacists should be allowed to prescribe cytisinicline.

Cytisinicline has more than 50 years of clinical experience and has a good safety profile. It is available over the counter in some countries, such as Canada and those in Eastern Europe. Referrals to free smoking quit lines for behavioral therapy should be provided as part of the counseling provided by the pharmacist in writing the prescription.

Pharmacist-prescribing will expand access to this important therapy for the subset of patients with limited access to other health care providers in the US.

Recommendation 2

The FDA should provide an additional pathway for generic drug approval when the drug is approved elsewhere with extensive evidence of safety and efficacy outside the US.

The full FDA approval process from Phase I through two adequately powered Phase III studies, along with the regulatory process, is a time-consuming and expensive process. It represents a disincentive to bring such drugs to market in the US. Furthermore, given the expense of this process, manufacturers who bring a drug to market must charge high prices to recoup their investment. Offering a third path that requires fewer or no clinical trials could increase access to effective therapies in the United States and help limit the rise in health care costs.

Recommendation 3

The FDA should encourage moving safe drugs with important public health impacts, like cytisinicline, to over the counter status.

Nicotine replacement therapy is already available over the counter, which allows smokers to make a quit attempt using NRT without the intervention of a health care provider. Cytisinicline is already available over the counter in Canada, Portugal, Spain, Italy, and Poland. Quickly moving cytisinicline to over the counter status could improve uptake among hard to reach smokers and help sustain the steady decline in the percentage of Americans who smoke cigarettes.

Recommendation 4

Cytisinicline should be studied in populations excluded from the Phase III clinical trials.

This includes patients with psychiatric illness, recent heart attacks, and pregnant patients. Randomized trials are not needed. Observational data demonstrating safety and efficacy in these populations should be sufficient to extend the indication for cytisinicline to these populations.

Patients with psychiatric illness have particular difficulty with smoking cessation. The combination of cytisinicline with behavioral therapy tailored to this population could provide a real advance in smoking cessation.

Patients with a recent myocardial infarction (MI) were excluded from many smoking cessation trials, but experts told us that they did not think that this is necessary. On the contrary, these patients are often particularly motivated to quit, so additional data in this population on safety and efficacy could then be folded into existing cardiac rehabilitation programs, which have already been shown to prevent recurrent cardiovascular (CV) events and death for patients with recent heart attacks.

Pregnant women have new motivations for smoking cessation. Quitting smoking during pregnancy benefits both mother and baby by reducing risks of premature birth, low birth weight, sudden infant death syndrome, respiratory issues, and birth defects. Real-world evidence from other parts of the world may provide evidence on the risks and benefits of cytisinicline in pregnant women.

Preliminary evidence suggests that varenicline is not teratogenic, but it remains class C (risk cannot be ruled out).

Recommendation 5

There should be additional studies on the optimal duration of therapy for cytisinicline.

There is uncertainty about the optimal duration of therapy for cytisinicline. Studies found that 12 weeks of treatment was superior to six weeks. It is possible that longer therapy would be even more effective because it both decreases cravings and blunts the rewards of nicotine. Additionally, varenicline, which shares the same mechanism of action as cytisinicline, is often used for longer than 12 weeks. Long-term safety data submitted to the FDA apparently suggest no safety concerns when cytisinicline is taken for at least one year. There is a need for additional longer-term studies to evaluate the net benefits of cytisinicline for more than 12 weeks.

Recommendation 6

Perform a head-to-head trial of cytisinicline with varenicline.

There is indirect evidence from network meta-analyses that cytisinicline and varenicline have similar efficacy and adverse events (apart from nausea). Only data from a well-done randomized trial can clarify whether one of the therapies has important advantages, either in efficacy or safety. This would be an ideal study for PCORI to support as the manufacturers have minimal incentives to support such a study.

Recommendation 7

Complete the ORCA-V2 Study

There is limited evidence about the clinical benefits of cytisinicline in people who vape nicotine. While the preliminary data from the ORCA-V1 study are promising, further study is needed. We look forward to the results from the definitive ORCA-V2 trial on the efficacy of cytisinicline in helping patients using nicotine-containing e-cigarettes to quit using them. Additionally, the harms of vaping remain controversial, so the health benefits of quitting vaping are uncertain (recommendation 8).

Recommendation 8

Expand research on measuring the clinical impact of nicotine e-cigarettes (vaping).

Many people do not like feeling addicted to nicotine, whether through cigarettes, e-cigarettes, oral pouches or other delivery systems. Early evidence supports significant clinical harms from inhaling the components of e-cigarettes, but the literature is not mature. Additional evidence is needed to carefully describe the full range of potential harms from e-cigarette use. This is particularly

important as some people advocate the use of e-cigarettes as an aid to smoking cessation. In addition, e-cigarette use may be a gateway to cigarette smoking, which is unequivocally harmful.

Recommendation 9

Pursue research on the impact of financial compensation for smoking cessation.

Contingency management has been an approach that has shown promise in treating stimulant use disorders, a very challenging set of addictions. It involves giving small rewards (gift cards, vouchers) when specific goals are met, such as a negative test for the drug – in this case cotinine in the urine or carbon monoxide on breath testing. This could be a useful approach to smoking cessation in populations who have not successfully quit using other approaches.

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Supplemental Materials

A. Background: Supplemental Information

A1. Definitions

Continuous Abstinence: No smoking throughout the follow-up period (e.g., six or 12 months), as self-reported and biochemically verified at multiple time points.[58]

Carbon Monoxide (CO) Biochemical Verification: Expired air carbon monoxide (CO) is the preferred method for verifying smoking abstinence. The usual cut-off point is nine parts per million (ppm), with readings of 10 ppm or more indicating smoking, usually within the last 24 hours. Although CO levels detect only recent smoking, most individuals who relapse return to regular smoking, making CO monitoring a useful tool for increasing the accuracy of self-reported abstinence.[58,59]

Cotinine Levels: Cotinine is found in the urine, saliva, and plasma of smokers, with a typical cut-off of 15 ng/mL for saliva or 50 ng/mL for urine. Cotinine levels do not distinguish between smoking and the use of nicotine replacement products. Therefore, while cotinine concentration is more sensitive, CO verification is preferred.[58]

Point-Prevalence Abstinence: No smoking at the time of follow-up or within the 'point' window (e.g., in the last seven or 30 days).[58]

Fagerström Test for Nicotine Dependence (FTND): A six-item self-report measure of the physical intensity of nicotine dependence. The total score ranges from 0 to 10, with higher scores indicating greater physical dependence on nicotine. Higher levels of dependence are associated with a lower likelihood of achieving abstinence during a quit attempt. The FTND was renamed as the Fagerström Test for Cigarette Dependence, but will be referred to as FTND throughout our report for consistency with the trials.[60,61]

Penn State Electronic Cigarette Dependence Index (ECDI): A 10-item self-report measure of the intensity of dependence on electronic cigarettes. The total score ranges from 0 to 20, with a score of 13 or higher indicating high dependence.[62]

Other Relevant Definitions

Absolute and Proportional Shortfalls: Absolute and proportional shortfalls are empirical measurements that capture different aspects of society's instincts for prioritization related to the severity or burden of an illness. The absolute shortfall is defined as the total absolute amount of future health patients with a condition are expected to lose without the treatment that is being assessed.[63] The ethical consequences of using absolute shortfall to prioritize treatments is that conditions that cause early death or that have very serious lifelong effects on quality of life receive the greatest prioritization. Thus, certain kinds of treatments, such as treatments for rapidly fatal

conditions of children, or for lifelong disabling conditions, score highest on the scale of absolute shortfall. The proportional shortfall is measured by calculating the proportion of the total health units of remaining life expectancy that would be lost due to untreated illness.[64,65] The proportional shortfall reflects the ethical instinct to prioritize treatments for patients whose illness would rob them of a large percentage of their expected remaining lifetime. As with absolute shortfall, rapidly fatal conditions of childhood have high proportional shortfalls, but high numbers can also often arise from severe conditions among older adults who may have only a few years left of average life expectancy but would lose much of that to the illness without treatment. Details on how to calculate the absolute and proportional QALY and evLY shortfalls can be found in ICER's reference case. Shortfalls will be highlighted when asking the independent appraisal committees to vote on unmet need despite current treatment options as part of characterizing a treatment's benefits beyond health and special ethical priorities (Section 5).

Health Improvement Distribution Index (HIDI): The HIDI identifies a subpopulation that has a higher prevalence of the disease of interest and therefore, creates an opportunity for proportionately more health gains within the subpopulation. This opportunity may be realized by achieving equal access both within and outside the identified subpopulation to an intervention that is known to improve health. The HIDI is defined as the disease prevalence in the subpopulation divided by the disease prevalence in the overall population. For example, if a disease has a prevalence of 10% among Black Americans whereas the disease prevalence among all Americans is 4%, then the Health Improvement Distribution Index is 10%/4%=2.5. In this example, a HIDI of 2.5 means that Black Americans as a subpopulation would benefit more on a relative basis (2.5 times more) from a new effective intervention compared with the overall population. HIDIs above one suggest that more health may be gained on the relative scale in the subpopulation of interest when compared to the population as a whole. The HIDI may be helpful in characterizing a treatment's benefits beyond health and special ethical priorities (Section 5).

In 2023, an estimated 11% of US adults reported cigarette smoking.[66] Table A1.1 provides estimates of cigarette smoking by race/ethnicity among US adults in 2023 using data from the National Health Interview Survey supplied by the CDC National Center for Health Statistics, with the corresponding HIDI calculation.

The prevalence of current cigarette smoking was the highest in American Indian and Alaska Native adults (15.4%) and this group may benefit 1.4 times more than the overall population from access to effective smoking cessation medications.

Table A1.1. Health Improvement Distribution Index Estimates for Adult US Smokers, 2023

Race/Ethnicity	Subgroup Estimate, %	Population Estimate, %	Subgroup Health Improvement Distribution Index
NH White	12.4	11.0	1.13
NH Black or African American	12.0		1.09
Hispanic or Latino	8.1		0.74
NH American Indian or Alaska Native	15.4		1.40
NH Asian	5.3		0.48
NH Multirace (2 or More)	11.7		1.06

NH: non-Hispanic, US: United States

A2. Potential Cost-Saving Measures in Smoking Cessation

ICER includes in its reports information on wasteful or lower-value services in the same clinical area that could be reduced or eliminated to create headroom in health care budgets for higher-value innovative services (for more information, please reference ICER's Value Assessment Framework). These services are ones that would not be directly affected by therapies for smoking cessation (e.g., costs of treating lung cancer), as these services will be captured in the economic model. Rather, we are seeking services used in the current management of smoking cessation beyond the potential offsets that arise from a new intervention. During stakeholder engagement and public comment periods, ICER encouraged all stakeholders to suggest services (including treatments and mechanisms of care) currently used for patients with smoking cessation that could be reduced, eliminated, or made more efficient. No suggestions were received.

A3. Patient Input on Clinical Trial Design

Manufacturers were asked to submit a written explanation of how they engaged patients in the design of their clinical trials, including the methods used to gather patient experience data and how they determined the outcomes that matter most to patients. ICER did not receive any feedback on this inquiry.

B. Patient Community Insights: Supplemental Information

B1. Methods

We spoke with people who smoke who had tried or had been offered all the options considered as comparators in this review, as well as users of electronic cigarettes. We spoke with patient advocates from the Truth Initiative and the COPD Foundation. Finally, we spoke with experts from the American Thoracic Society.

C. Clinical Guidelines

We focused on extracting the recommendations for pharmacotherapy for smoking cessation and highlighted any recommendations for cytisine/cytisinicline.

World Health Organization 2024

WHO recommends varenicline, NRT, bupropion and **cytisine** as treatment options for tobacco users who smoke and are interested in quitting. Their first line options are varenicline, NRT, or bupropion.

United States Preventive Services Task Force 2021

The USPSTF gave an A rating (high certainty that the net benefit is substantial) to FDA-approved pharmacotherapy for smoking cessation to nonpregnant adults who use tobacco. These therapies are NRT, bupropion, and varenicline.

American Thoracic Society 2020

ATS strongly recommends varenicline as first-line therapy over bupropion and NRT, including in patients who are not yet ready to quit and in patients with comorbid mental health diagnoses (substance use disorder, depression, anxiety, schizophrenia and bipolar disorder).

NICE 2025 update to 2021 Guideline

NICE recommends access to **cytisinicline**, NRT, varenicline, bupropion, and nicotine-containing electronic cigarettes to all adults who smoke cigarettes.

Canadian Task Force on Preventive Health Care 2025

The Canadian task force made strong recommendations for the use of bupropion, **cytisine**, NRT and varenicline with estimates of benefit being large for varenicline, moderate for **cytisine** and NRT, and small to moderate for bupropion.

D. Comparative Clinical Effectiveness: Supplemental Information

D1. Detailed Methods

PICOTS

Population

The primary population for the review is individuals who are interested in quitting cigarettes.

In addition, we explored data in the population of individuals interested in quitting electronic cigarettes (vaping).

When possible, we evaluated the evidence for treatment effect modification by subpopulations defined by:

- Sociodemographic factors (e.g., sex, race/ethnicity, education, income)
- Pregnant and postpartum women
- Age (e.g., <18 years, ≥18 years)
- Psychiatric disorders (e.g., schizophrenia, depression, substance use disorders)

Interventions

- Cytisinicline with behavioral support

Systematic reviews have demonstrated that combining behavioral interventions with pharmacotherapy is more effective than pharmacotherapy alone.[67,68] All of the ORCA trials of cytisinicline included behavioral support.

Comparators

We compared cytisinicline to the following:

- No pharmacotherapy/behavioral support alone (placebo arm)
- Each of the following in combination with behavioral support:
    - Nicotine replacement therapy (NRT) products (e.g., nicotine patch plus a short-acting NRT such a gum or lozenge)
    - Electronic cigarettes containing nicotine (for smoking cessation)
    - Varenicline
    - Varenicline plus NRT
    - Bupropion

Outcomes

The outcomes of interest are described in the list below.

- Patient-Important Outcomes
    - Abstinence from cigarette smoking or a decrease in cigarettes smoked per day
    - Adverse events including
        - Nausea
        - Headaches
        - Sleep disturbances (e.g., vivid dreams, insomnia)
        - Serious adverse events
        - Adverse events leading to treatment discontinuation
        - Adverse effects of quitting smoking

Timing

Evidence on intervention effectiveness and harms were derived from studies of at least six months duration.

Settings

All relevant settings were considered.

Table D1.1. PRISMA 2020 Checklist

Section and Topic	Item #	Checklist Item
TITLE		
Title	1	Identify the report as a systematic review.
ABSTRACT		
Abstract	2	See the PRISMA 2020 for Abstracts checklist.
INTRODUCTION		
Rationale	3	Describe the rationale for the review in the context of existing knowledge.
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.
METHODS		
Eligibility Criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.
Information Sources	6	Specify all databases, registers, websites, organizations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.
Search Strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.
Selection Process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.
Data Collection Process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.
Data Items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.
Study Risk of Bias Assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.
Effect Measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.
Synthesis Methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.

Section and Topic	Item #	Checklist Item
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.
Reporting Bias Assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).
Certainty Assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.
RESULTS		
Study Selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.
Study Characteristics	17	Cite each included study and present its characteristics.
Risk of Bias in Studies	18	Present assessments of risk of bias for each included study.
Results of Individual Studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.
Results of Syntheses	20a	For each synthesis, briefly summarize the characteristics and risk of bias among contributing studies.
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g., confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.
	20c	Present results of all investigations of possible causes of heterogeneity among study results.
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.
Reporting Biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.
Certainty of Evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.
DISCUSSION		
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.
	23b	Discuss any limitations of the evidence included in the review.
	23c	Discuss any limitations of the review processes used.
	23d	Discuss implications of the results for practice, policy, and future research.

Section and Topic	Item #	Checklist Item
OTHER INFORMATION		
Registration and Protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.
	24c	Describe and explain any amendments to information provided at registration or in the protocol.
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.
Competing Interests	26	Declare any competing interests of review authors.
Availability of Data, Code, and Other Materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.

From: Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *PLoS Med.* 2021;18(3):e1003583.

Data Sources and Searches

Procedures for the systematic literature review assessing the evidence on new therapies for smoking cessation followed established best research methods.[69,70] We reported the review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[71] The PRISMA guidelines include a checklist of 27 items (see Table D1.1).

We searched MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials for relevant studies in June 2025. Each search was limited to English-language studies of human subjects and excluded articles indexed as guidelines, letters, editorials, narrative reviews, case reports, or news items. We included abstracts from conference proceedings identified from the systematic literature search. All search strategies were generated utilizing the Population, Intervention, Comparator, and Study Design elements described above. The proposed search strategies included a combination of indexing terms (MeSH terms in MEDLINE and EMTREE terms in EMBASE), as well as free-text terms.

To supplement the database searches, we performed manual checks of the reference lists of included trials and systematic reviews and invited key stakeholders to share references germane to the scope of this project. We also supplemented our review of published studies with data from conference proceedings, regulatory documents, information submitted by manufacturers, and other grey literature when the evidence met ICER standards (for more information, see the Policy on Inclusion of Grey Literature in Evidence Reviews.

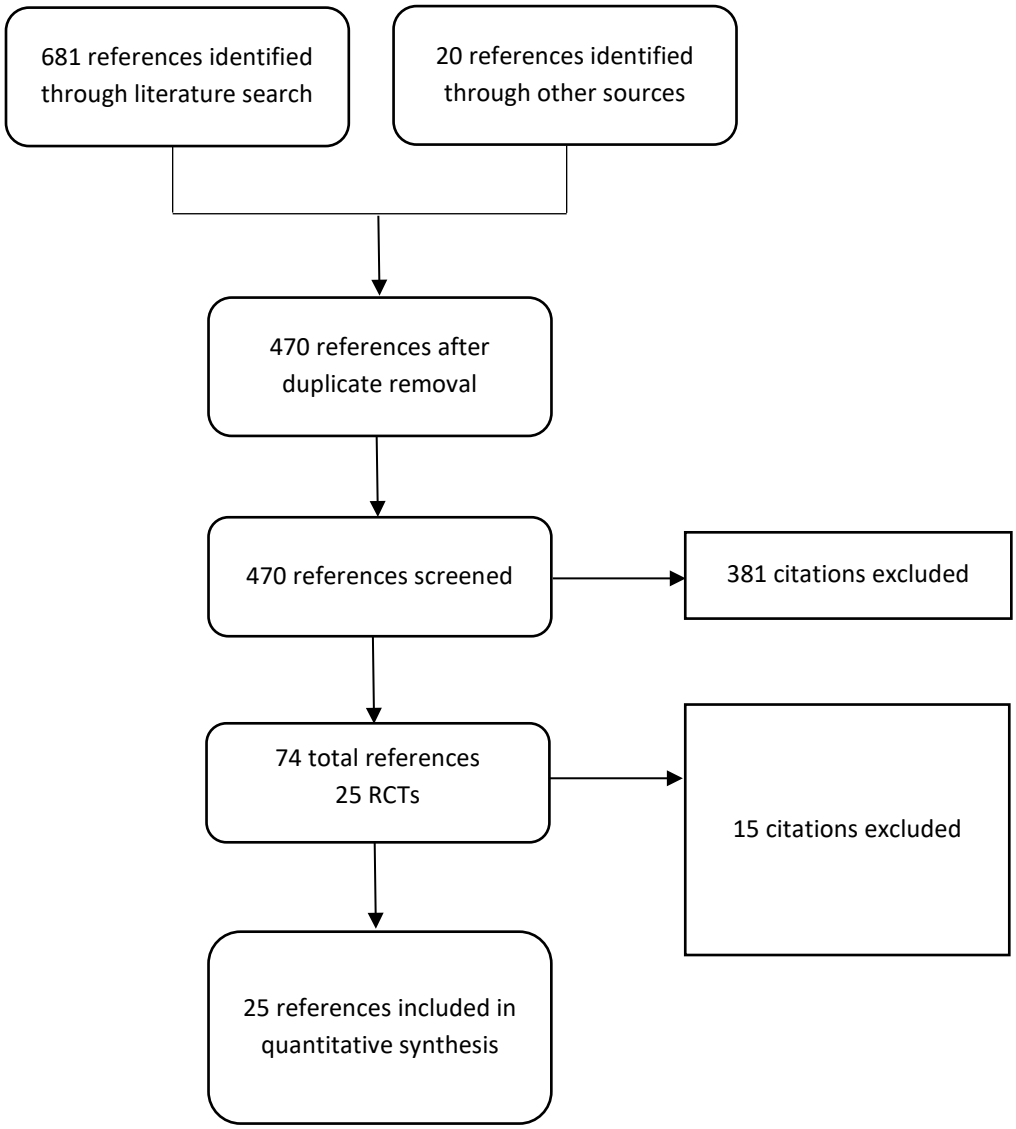
Table D1.2. Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R) 1946 to Present, Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews Search Strategy for Cytisinicline for Smoking Cessation

1	exp smoking cessation/
2	(‘Cessation, Smoking’ or ‘Smoking Cessation*’ or ‘Giving Up Smoking’ or ‘Smoking, Giving Up’ or ‘Smokings, Giving Up’ or ‘Up Smoking, Giving’ or ‘Quitting Smoking’ or ‘Smoking, Quitting’ or ‘Stopping Smoking’ or ‘Smoking, Stopping’).ti,ab.
3	1 or 2
4	('Cytisine*' or ‘cytisinicline’ or 'Tabex').ti,ab.
5	(‘Varenicline*’ or ‘Chantix’ or ‘Champix’).ti,ab.
6	(‘Bupropion*’ or ‘Amfebutamone’ or ‘Zyban*’ or ‘Wellbutrin’ or ‘Quomen’ or ‘Zyntabac’).ti,ab.
7	('Nicotine Replacement Therap*' or 'Nicotine Patch*' or 'Nicotine Transdermal Patch*' or 'Transdermal Patch, Nicotine' or 'Nicotine Replacement Product*' or 'Replacement Product*, Nicotine' or 'Smoking Cessation Product*' or 'Nicotine Lozenge*' or 'Lozenge*, Nicotine' or 'Nicotine Inhalant*' or 'Inhalant*, Nicotine' or 'Nicotine Nasal Spray*' or 'Nasal Spray*, Nicotine' or 'Spray*, Nicotine Nasal' or 'Nicotine Polacrilex' or 'Polacrilex, Nicotine' or 'Nicotine Delivery Device*' or 'Delivery Device*, Nicotine' or 'Device*, Nicotine Delivery' or 'Chewing Gum, Nicotine' or 'Nicotine Chewing Gum*' or 'Nicorette').ti,ab.
8	('Electronic Nicotine Delivery System*' or 'Electronic Cigarette*' or 'Cigarette*, Electronic' or 'E-Cig*' or 'E Cig*').ti,ab.
9	4 or 5 or 6 or 7 or 8
10	3 and 9
11	10 and (exp randomized controlled trial/ OR exp systematic review)
12	(animals not (humans and animals)).sh.
13	11 not 12
14	13 not (addresses OR autobiography OR bibliography OR biography OR congresses OR consensus development conference OR dictionary OR directory OR duplicate publication OR editorial OR encyclopedia OR interactive tutorial OR observational study OR case series).pt
15	Limit 14 to English language
16	Remove duplicates from 15
17	limit 16 to yr="2022 -Current"

Table D1.3. EMBASE Search Strategy for Cytisinicline for Smoking Cessation

1	'smoking cessation'/exp
2	('abstination, smoking' OR 'abstinence from nicotine' OR 'abstinence from smoking' OR 'abstinence from tobacco' OR 'cessation, smoking' OR 'dehabituation, smoking' OR 'nicotine abstination' OR 'nicotine abstinence' OR 'nicotine cessation' OR 'nicotine withdrawal' OR 'quit smoking' OR 'smoking abstinence' OR 'smoking dehabituation' OR 'smoking, stopping' OR 'stop smoking' OR 'stopping smoking' OR 'tobacco use cessation' OR 'smoking cessation'):ti,ab
3	#1 OR #2
4	('baptitoxin' OR 'baptitoxine' OR 'belnifrem' OR 'citizin' OR 'cytisine' OR 'cytiton' OR 'cytitone' OR 'cytizin' OR 'desmoxan' OR 'glavrinxa' OR 'laburnin' OR 'laburnine' OR 'levo cytisine' OR 'sophorine' OR 'tabex' OR 'tsitizin' OR 'ulexin' OR 'ulexine' OR 'cytisinicline'):ti,ab
5	('champix' OR 'chantix' OR 'vareniclin' OR 'vareniclin tartrat' OR 'varenicline citrate' OR 'varenicline tartrate' OR 'varenicline'):ti,ab
6	('amfebutamone hydrochloride' OR 'aplenzin' OR 'budeprion' OR 'budeprion xl' OR 'buprion hydrochloride' OR 'bupropin' OR 'bupropion' OR 'bupropion hydrobromide' OR 'bupropion hydrochloride' OR 'bupropion xl' OR 'buproprion' OR 'buxon' OR 'odranal' OR 'quomem' OR 'quomen' OR 'wellbatrin' OR 'wellbutrin' OR 'wellbutrin retard' OR 'wellbutrin sr' OR 'wellbutrin xl' OR 'wellbutrin xr' OR 'zyban' OR 'zyban lp' OR 'zyban sr' OR 'zyban sr refill' OR 'zyban sustained release' OR 'amfebutamone'):ti,ab
7	('nicotine replacement therapy' OR 'nicotine patch' OR 'chewing gum, nicotine' OR 'commit (drug)' OR 'nicorama' OR 'nicorette' OR 'nicorette (mint)' OR 'nicorette (orange)' OR 'nicorette plus' OR 'nicotine chewing gum' OR 'nicotine polacrilex' OR 'nicotine polacrilex (mint)' OR 'nicotine polacrilex (orange)' OR 'nicotine resinate' OR 'nicotinell 2' OR 'thrive (drug)' OR 'tobacco use cessation devices' OR 'tobacco use cessation product' OR 'tobacco use cessation products' OR 'nicotine gum' OR 'nicotine lozenge'):ti,ab
8	('e cigarette' OR 'e cigarettes' OR 'electronic cigarettes' OR 'electronic nicotine delivery system' OR 'electronic nicotine delivery systems' OR 'electronic cigarette'):ti,ab
9	#4 OR #5 OR #6 OR #7 OR #8
10	#3 AND #9
11	#10 AND ('phase 3 clinical trial'/de OR 'randomized controlled trial'/de OR 'randomized controlled trial topic'/de OR 'systematic review'/de)
12	('animal'/exp OR 'nonhuman'/exp OR 'animal experiment'/exp) NOT 'human'/exp
13	#11 NOT #12
14	#13 NOT ('addresses'/it OR 'autobiography'/it OR 'bibliography'/it OR 'biography'/it OR 'case report'/it OR 'comment'/it OR 'congresses'/it OR 'consensus development conference'/it OR 'duplicate publication'/it OR 'editorial'/it OR 'guideline'/it OR 'in vitro'/it OR 'interview'/it OR 'lecture'/it OR 'legal cases'/it OR 'legislation'/it OR 'letter'/it OR 'news'/it OR 'newspaper article'/it OR 'note'/it OR 'patient education handout'/it OR 'periodical index'/it OR 'personal narratives'/it OR 'portraits'/it OR 'practice guideline'/it OR 'short survey'/it OR 'video audio media'/it OR 'observational study'/it OR 'case study'/it)
15	#14 AND [English]/lim
16	#15 AND [medline]/lim
17	#16 AND [2022-01-01]/sd

Figure D1.1. PRISMA Flow Chart Showing Results of Literature Search for Smoking Cessation



Study Selection

We performed screening at both the abstract and full-text level. Two investigators independently screened all titles and abstracts identified through electronic searches according to the inclusion and exclusion criteria described earlier using Nested Knowledge (Nested Knowledge, Inc, St. Paul, Minnesota); a third reviewer worked with the initial two reviewers to resolve any issues of disagreement through consensus. We did not exclude any study at abstract-level screening due to insufficient information. For example, an abstract that did not report an outcome of interest would be accepted for further review in full text. We retrieved the citations that were accepted during abstract-level screening for full text appraisal. One investigator reviewed full papers and provided justification for exclusion of each excluded study.

Data Extraction

Data were extracted into Microsoft Word and Excel. The basic design and elements of the extraction forms followed those used for other ICER reports. Elements included a description of patient populations, sample size, duration of follow-up, funding source, study design features, interventions (agent, dosage, frequency, schedules), concomitant therapy allowed and used (agent, dosage, frequency, schedules), outcome assessments, results, and risk of bias for each study. The data extraction was performed in the following steps:

1. One reviewer extracted information from the full articles, and a second reviewer validated the extracted data.
2. Extracted data were reviewed for logic, and a random proportion of data were validated by a third investigator for additional quality assurance.

Risk of Bias Assessment

We examined the risk of bias for each randomized trial contributing to the smoking and vaping cessation NMAs using criteria published in the Cochrane Risk of Bias Assessment Tool Version 2.[70,72] Risk of bias was assessed for each of the following aspects of the trials: randomization process, deviation from the intended interventions, missing outcome data, measurement of the outcome, selection of the reported results, and overall risk of bias. Two reviewers independently assessed these domains. Any disagreements were resolved through discussion or by consulting a third reviewer. We did not assess the risk of bias in trials where we only had access to conference abstracts/presentations.

To assess the risk of bias in trials, we rated the categories as: “low risk of bias,” “some concerns,” or “high risk of bias.” Guidance for risk of bias ratings using these criteria is presented below:

Low risk of bias*: The study is judged to be at low risk of bias for all domains for this result.*

Some concerns*: The study is judged to raise some concerns in at least one domain for this result, but not to be at high risk of bias for any domain.*

High risk of bias*: The study is judged to be at high risk of bias in at least one domain for this result or the study is judged to have some concerns for multiple domains in a way that substantially lowers confidence in the result.*

We examined the risk of bias for the outcomes of continuous abstinence weeks 9 to 24 smoking abstinence and seven-day point prevalence vaping abstinence. See Table D1.3.

Table D1.4. Cochrane Risk of Bias Assessment 2 for Continuous Abstinence Weeks 9 to 24 Outcome in Smoking Cessation Trials

Study (Author, Year)	Randomization Process	Deviation from the Intended Interventions	Missing Outcome Data	Measurement of the Outcome	Selection of the Reported Result	Overall Risk of Bias
Cytisinicline						
ORCA-2 (Rigotti, 2023)[11]	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
ORCA-3 (Rigotti, 2025)[12]	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Varenicline						
NCT00141206 (Gonzalez, 2006)	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
NCT00143364 (Jorenby, 2006)	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
NCT00139750 (Nakamura, 2007)	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
NCT00141167 (Tsai, 2007)	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
NCT00150228 (Niaura, 2008)	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
NCT00371813 (Wang, 2009)	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
NCT00594204 (Bolliger, 2011)	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
NCT00691483 (Rennard, 2012)	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
NCT00507728 (Cinciripini, 2013)	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
NCT01244061 (Gonzalez, 2014)	Some Concerns	Some Concerns	Low Risk	Low Risk	Low Risk	Some Concerns
NCT01456936 (Anthenelli, 2016)	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk

Study (Author, Year)	Randomization Process	Deviation from the Intended Interventions	Missing Outcome Data	Measurement of the Outcome	Selection of the Reported Result	Overall Risk of Bias
NCT00918307 (Mercié, 2018)	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
NCT01710137 (Ashare, 2019)	Some Concerns	Low Risk	Low Risk	Low Risk	Low Risk	Some Concerns
NCT01387425 (Russo, 2022)[73]	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk

Table D1.5 Cochrane Risk of Bias Assessment 2 for Point Prevalence Abstinence Outcome in Vaping Cessation Trials

Studies (Author, Year)	Randomization Process	Deviation from the Intended Interventions	Missing Outcome Data	Measurement of the Outcome	Selection of the Reported Result	Overall Risk of Bias
Cytisinicline						
ORCA V-1 (Rigotti, 2024)[17]	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Varenicline						
VAREVAPE (Caponnetto, 2023)[19]	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
ViVA (Evins, 2025)[18]	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk

Evaluation of Clinical Trial Diversity

We evaluated the demographic diversity of clinical trials using the ICER-developed Clinical trial Diversity Rating (CDR) Tool.[74] The CDR tool was designed to evaluate the three demographic characteristics described in Table D1.5. Representation for each demographic category was evaluated by quantitatively comparing clinical trial participants with disease-specific prevalence estimates,[75] using the metric "Participant to Disease-prevalence Representation Ratio" (PDRR). Next, a representation score between 0 to 3 was assigned based on the PDRR estimate (See Table D1.6 for the PDRR cut points that correspond to each representation score). Finally, based on the total score of the demographic characteristics (e.g., race and ethnicity), the categories "Good," "Fair," or "Poor" are used to communicate the overall level of diversity of a clinical trial. The description of the rating categories for each demographic characteristic is provided in Table D1.7.

Table D1.6. Demographic Characteristics and Categories

Demographic Characteristics	Categories
1. Race and Ethnicity*	Racial categories: • White • Black or African American • Asian • American Indian and Alaskan Native • Native Hawaiian and Other Pacific Islanders Ethnic Category: • Hispanic or Latino
2. Sex	• Female • Male
3. Age	• Older adults (≥65 years)

*Multinational trials: For multinational clinical trials, our approach is to evaluate only the subpopulation of patients enrolled from the US on racial and ethnic diversity

Table D1.7. Representation Score

PDRR	Score
0	0
>0 and Less Than 0.5	1
0.5 to 0.8	2
≥0.8	3

PDRR: Participant to Disease-prevalence Representation Ratio

We identified prevalence data for race/ethnicity, sex, and age of adult cigarette smokers in the United States from the Center for Disease Control's (CDC) 2022 National Health Interview Survey on Tobacco Product Use Among Adults in the United States.[75] We converted the CDC data into prevalence estimates (adjusted to the US census population) for use in our CDR tool. The trials did not provide data by age groups, and as such we did not assess the trials on representation of older adults.

Table D1.8. Rating Categories

Demographic Characteristics	Demographic Categories	Maximum Score	Rating Categories (Total Score)
Race and Ethnicity*	Asian, Black or African American, White, and Hispanic or Latino	12	Good (11-12) Fair (7-10) Poor (≤6)
Sex	Male and Female	6	Good (6) Fair (5) Poor (≤4)
Age	Older adults (≥65 years)	3	Good (3) Fair (2) Poor (≤1)

*American Indian or Alaskan Native & Native Hawaiian or Other Pacific Islander are not factored into the overall racial and diversity rating. However, information on enrollment and PDRR estimates are reported when reliable prevalence estimates are available.

Results: Cigarette Smoker Population

Table D1.9. Race and Ethnicity

	White	Black/ African American	Asian	Hispanic/ Latino	Total Score	Diversity Rating	AIAN	NHPI
Prevalence[75]	82.7%	16.7%	2.5%	13.2%	-	-	2.2%	NR
ORCA-2[11]	81.40%	16.00%	0.40%	8.40%	-	-	0.5%	0.5%
PDRR	0.98	0.96	0.16	0.64	-	-	0.23	NC
Score	3	3	1	2	9	Fair	NC	NC
ORCA-3[12]	80.00%	18.00%	0.5%	5.70%	-	-	0.63%	0.3%
PDRR	0.97	1.08	0.20	0.43	-	-	0.29	NC
Score	3	3	1	1	8	Fair	NC	NC

AIAN: American Indian or Alaskan Native, NC: Not calculated, NR: Not reported, NHPI: Native Hawaiian or Pacific Islander, PDRR: Participant to Disease-prevalence Representation Ratio

*CDC data was converted into prevalence estimates (adjusted to the US census population) for use in our CDR tool.

Race and Ethnicity: Both trials received a "fair" rating due to the underrepresentation of Asian and Hispanic participants.

Table D1.10. Sex and Age

	Sex				Age		
	Male	Female	Score	Rating	Older Adults (≥65 Years)	Score	Rating
Prevalence[75]	57.4%	43.5%	-	-	16.6%	-	-
ORCA-2[11]	45.40%	54.60%	-	-	NR	-	-
PDRR	0.79	1.26	-	-	NC	-	-
Score	2	3	5	Fair	NC		
ORCA-3[12]	44.60%	55.40%	-	-	NR	-	-
PDRR	0.78	1.27	-	-	NC	-	-
Score	2	3	5	Fair	NC	NC	NC

NC: Not calculated, NR: Not reported, PDRR: Participant to Disease-prevalence Representation Ratio

*CDC data was converted into prevalence estimates (adjusted to the US census population) for use in our CDR tool.

Sex: Both trials achieved a "fair" rating for representation of male and female participants because of lower representation of male smokers in the trials compared with smokers overall.

Assessment of Level of Certainty in Evidence

We used the ICER Evidence Rating Matrix to evaluate the level of certainty in the available evidence of a net health benefit among each of the interventions of focus.[76,77]

Assessment of Bias

As part of our quality assessment, we evaluated the evidence base for the presence of potential publication bias. We performed an assessment of publication bias for cytisinicline and other therapies in our scope using ClinicalTrials.gov. Search terms included "cytisinicline", “cytisine”, “varenicline", “chantix”, "bupropion", “zyban”, “nicotine replacement therapy”, and “electronic cigarettes”.

We did not identify any studies that would have met our inclusion criteria, and for which no findings have been published.

D2. Data Synthesis and Statistical Analyses

Feasibility of Conducting Meta-Analysis and/or Network Meta-Analysis

We examined the feasibility of conducting quantitative analyses across three of our research questions.

For Research Question 1 (net health benefit of cytisinicline with behavioral support versus no pharmacotherapy/behavioral support alone), the identical trial design of the two pivotal trials of cytisinicline, ORCA-2 and 3, allowed for a meta-analysis to synthesize direct evidence on the drug's efficacy and harms.

For Research Questions 2 and 8 (net health benefit of cytisinicline with behavioral support vs. varenicline plus behavioral support), we considered an NMA because direct evidence for the comparative efficacy of cytisinicline (3 mg TID for 12 weeks) versus varenicline (12-week standard course) for smoking or vaping cessation were not available. We examined differences in study populations, study design, intervention type, outcome definition and measurement, and analytic methods, as well as quality/risk of bias of these studies. Our smoking NMA included 22 trials that were deemed sufficiently similar, while the vaping cessation NMA included three studies. Details of the NMA methods are described below.

All data analyses were validated by an independent member of the research team. The validator reviewed and confirmed the data analysis methods, data format, and analysis code. The validator re-ran the analysis, validated the results, and confirmed the appropriateness of reported data.

NMA Methods

Question 1

A Mantel-Haenszel pairwise meta-analysis was performed using evidence from ORCA 2 and 3 trials on the outcomes of continuous abstinence from smoking between weeks 9 and 12 (primary study outcome) and weeks 9 to 24 (secondary study outcome), as well as tolerability/safety events including abnormal dreams, insomnia, headache, nausea, discontinuation due to adverse events, and serious adverse events. These binary outcomes were represented by pooled risk ratios and risk differences; both were reported with associated 95% confidence intervals in Tables XX and XX in the main report. Meta-analyses were conducted using R Statistical Software (version 4.2.1) with the following data packages: dmetar, tidyverse, and meta. Given the identical study design of the two trials, we reported on the fixed-effects results of the meta-analyses in the main report. A comparison between the fixed-effects and random-effects models are provided below (Table D2.1). None of the comparisons reported significant levels of heterogeneity as measured by the I^2 statistic.

We excluded previous placebo-controlled studies of cytisinicline due to differences in dosages and treatment duration, which were most often a 25-day treatment regimen involving a downward titration starting with 9 mg a day (six 1.5 mg tablets).

Table D2.1. Fixed and Random Effects Meta-Analysis Results, Cytisinicline + Behavioral Support Versus Behavioral Support Alone

Binomial Outcomes	Risk Ratio (95% CI) Fixed-Effects Model	Risk Ratio (95% CI) Random-Effects Model	I^2, p-Value
CAR Weeks 9 to 12	**3.83 (2.81, 5.22)**	**3.80 (2.65, 5.46)**	25.7%, p = 0.25
CAR Weeks 9 to 24	**4.64 (3.04, 7.10)**	**4.64 (3.03, 7.09)**	0%, p = 0.79
Abnormal Dreams	**1.79 (1.09, 2.94)**	1.80 (0.94, 3.45)	38.9%, p = 0.20
Headache	1.14 (0.75, 1.73)	1.13 (0.74, 1.73)	0.0%, p = 0.39
Insomnia	**1.73 (1.15, 2.62)**	**1.73 (1.14, 2.61)**	0%, p = 0.56
Nausea	0.85 (0.54, 1.33)	0.85 (0.54, 1.33)	0%, p = 0.60
Discontinuation Due to AEs	2.15 (0.88, 5.23)	2.14 (0.88, 5.22)	0%, p = 0.67
Serious AEs	1.46 (0.68, 3.12)	1.47 (0.58, 3.73)	26.8%, p = 0.24

AE: Adverse event, CAR: Continuous abstinence rate, CI: Confidence Interval, I^2: Measure of heterogeneity

Question 2

In the NMA, we sought to include varenicline placebo-controlled studies that closely matched the inclusion/excluded criteria of the ORCA-2 and 3 trials. Eligible studies recruited adult smokers actively looking to quit smoking and were randomized to a standard 12-week course of varenicline or placebo in addition to some type of behavioral support, which typically consisted of brief 10-minute sessions with a smoking cessation counselor at site visits.

Table D2.2. Interventions in Network Meta-Analysis

Intervention	Detail
Cytisinicline	3 mg tablet taken three times daily (TID) for a period of 84 days (12 weeks)
Varenicline[78]	Days 1 – 3: 0.5 mg once daily Days 4 – 7: 0.5 mg twice daily Day 8 – end of treatment: 1 mg twice daily
Placebo/ Behavioral Support	Varies among trials. Typically consists of ~10 min counseling sessions during in-clinic visit.

mg: milligrams

We excluded studies whose trial population consisted of smokers not looking to quit smoking in the immediate future, had at least one disqualifying comorbidity, such as psychiatric (e.g., bipolar disorder, schizophrenia, depression), respiratory (e.g., COPD, asthma), and substance abuse (alcohol use disorder, opioid dependence). We included three studies where the smoker population had comorbidities not explicitly excluded by the criteria above. These studies involved smokers with type 2 diabetes (Russo 2022) and HIV (Ashare 2019, Mercie 2018).

Studies that would have met our criteria but did not include at least one of our outcomes of interest (continuous abstinence rate from weeks 9 to 24, or incidence of abnormal dreams, insomnia, headache, nausea, discontinuation due to adverse events, and serious adverse events) were excluded. Continuous abstinence rate at weeks 9 to 24 is a commonly reported outcome in smoking cessation trials and its duration satisfies our research protocol's interest in outcomes with 6 months of follow-up or longer.

A total of 22 randomized clinical trials met our inclusion criteria (Table D2.3). Some of the clinical trials did not contribute to each of the seven outcomes of interest; data availability for each trial is noted in the "NMA Contribution" column. For several safety outcomes, we used data from the combined psychiatric and non-psychiatric cohorts of the Anthenelli 2016 (EAGLES) trial because of limited reporting. Across the study arms, smokers were middle aged (40s or 50s), largely male (~61%), and had a moderate to high nicotine dependence.

NMAs were conducted using the indiRect NMA platform (EVERSANA). All outcomes were evaluated as dichotomous outcomes and were synthesized using a random-effects Bayesian NMA with binomial likelihood with a log link; analyses were based on burn-in and sampling of 50,000 iterations. All study outcomes were reported using risk ratio and risk difference values with 95% credible intervals.

Table D2.3. Smoking NMA Trial Baseline Characteristics (N=22)

Study	12-Week Treatment Arm	n	Age, Mean (SD)	Male, %	FTND Score, (SD)	NMA Contribution
NCT05206370 Rigotti 2025	Cytisinicline	264	52 (12)	43	5.6 (1.9)	All
	Placebo	265	51 (11)	45	5.6 (1.9)	
NCT04576949 Rigotti 2023	Cytisinicline	270	53 (12)	50	5.6 (1.9)	All
	Placebo	271	52 (12)	41	5.6 (1.7)	
NCT01387425 Russo 2022	Varenicline	150	57 (NR)	78	NR	All
	Placebo	150	57 (NR)	79	NR	
NCT02351167 Chen 2020	Varenicline	274	47 (11)	48	4.9 (2.0)	Headache, Nausea, Insomnia, Abnormal dreams, SAEs
	Placebo	273	47 (12)	41	4.8 (2.1)	
NCT01710137 Ashare 2019	Varenicline	89	49 (10)	72	NR	CAR 9-24, SAEs
	Placebo	90	49 (10)	64	NR	
NCT00918307 Mercie 2018	Varenicline	123	47 (9)	81	5.2 (2.0)	CAR 9-24, Discontinuation due to AEs, SAEs
	Placebo	124	44 (9)	84	5.5 (2.0)	
NCT00943618 Cinciripini 2018	Varenicline	166	49 (11)	59	4.7 (2.0)	All harms
	Placebo	56	48 (10)	57	5.3 (2.2)	
NCT01228175 Littlewood 2017	Varenicline	111	35 (10)	66	4.6 (2.0)	Headache, Nausea, Insomnia, Abnormal dreams, SAEs
	Placebo	94	34 (10)	66	4.7 (2.0)	

Study	12-Week Treatment Arm	n	Age, Mean (SD)	Male, %	FTND Score, (SD)	NMA Contribution
NCT01456936 Anthenelli 2016	Varenicline	990*	46 (13)	52	5.5 (2.0)	All
	Placebo	999*	46 (13)	49	5.5 (2.0)	
NCT01639560 Ebbert 2016	Varenicline	45	37 (12)	51	NR	Headache, Nausea, Discontinuation due to AEs, SAEs
	Placebo	48	37 (11)	39	NR	
NCT01314001 Lerman 2015	Varenicline	420	45 (12)	55	5.4 (2.0)	Headache, Nausea, Insomnia, Abnormal dreams, SAEs
	Placebo	408	46 (11)	57	5.1 (2.0)	
NCT01244061 Gonzales 2014	Varenicline	249	48 (11)	50	5.4 (2.0)	All
	Placebo	245	47 (11)	49	5.7 (2.0)	
NCT00507728 Cinciripini 2013	Varenicline	86	44 (11)	62	4.5 (2.2)	All
	Placebo	106	45 (11)	63	4.4 (2.2)	
NCT00691483 Rennard 2012	Varenicline	493	44 (13)	60	5.6 (2.2)	All harms
	Placebo	166	43 (12)	60	5.4 (2.1)	
NCT00594204 Bolliger 2011	Varenicline	390	43 (11)	58	6.0 (2.2)	All
	Placebo	198	44 (11)	66	6.1 (2.0)	
NCT00371813 Wang 2009	Varenicline	165	39 (NR)	96	5.3 (NR)	All
	Placebo	168	39 (NR)	97	5.5 (NR)	
NCT00150228 Niaura 2008	Varenicline	157	42 (11)	50	5.4 (NR)	All
	Placebo	155	42 (12)	54	5.4 (NR)	
NCT00139750 Nakamura 2007	Varenicline	130	40 (12)	79	5.4 (2.1)	CAR 9-24, Headache, Nausea, Insomnia, Discontinuation due to AEs, SAEs
	Placebo	129	40 (12)	76	5.7 (1.8)	
NCT00141167 Tsai 2007	Varenicline	126	40 (9)	85	5.2 (2.4)	All
	Placebo	124	41 (11)	93	5.0 (2.3)	
NCT00143364 Jorenby 2006	Varenicline	344	45 (11)	55	5.4 (2.2)	All**
	Placebo	341	42 (12)	58	5.2 (2.2)	
NCT00141206 Gonzales 2006	Varenicline	352	43 (11)	50	5.2 (2.2)	All**
	Placebo	344	43 (12)	54	5.4 (2.0)	
NCT00150254 Oncken 2006	Varenicline	130	42 (11)	49	5.3 (2.1)	All harms
	Placebo	129	43 (9)	52	5.8 (2.3)	

AEs: adverse events, CAR: continuous abstinence rate, FTND: Fagerström Test for Nicotine Dependence, N: number, NR: not reported, NMA: network meta-analysis, SD: standard deviation, SAEs: serious adverse events, *Nonpsychiatric cohort.

Assessing Model Fit

Random Effects Versus Fixed Effects Model

Given the heterogeneity among the trials with regards to the above patient characteristics, we assumed a priori that random-effects model would be more appropriate. To validate this decision, we explored both random-effects and fixed-effects model and assessed model fit in Table D2.4. We found the random-effects model to have an improved fit over the fixed-effects model in six of the seven outcomes, as measured by the Deviance Information Criterion (DIC).

Table D2.4. Model Fit Assessment, Random-Effects Versus Fixed Effects

Outcomes	Random Effects DIC	Fixed Effects DIC
CAR Weeks 9 to 24	223.34	230.67
Abnormal Dreams	229.43	246.41
Headache	259.01	259.93
Insomnia	251.92	258.41
Nausea	274.04	302.71
Discontinuation Due to AEs	198.7	199.06
Serious AEs	195.77	194.35

AE: Adverse event, CAR: Continuous Abstinence Rate, DIC: Deviance Information Criterion

Baseline Risk Adjustment

In selecting our base case analysis for the NMAs, we assessed the variations in baseline risk/ placebo response across the interventions and trials included for each of our seven outcomes of interest. We evaluated if a baseline-risk adjusted NMA provided a better fit than an unadjusted NMA for each outcome. The adjusted NMA was associated with improved fit relative the unadjusted model for four of the seven outcomes of interest: CAR at weeks 9 to 24, abnormal dreams, headache, and nausea. However, despite some changes in the magnitude of the relative risk between the unadjusted and adjusted models, there were no instances across any of seven outcomes for which the risk ratio (cytisinicline vs. varenicline) had a change in statistical significance between models.

Figure D2.1. Assessment of Baseline Risk (Continuous Abstinence Rate Weeks 9 to 24)

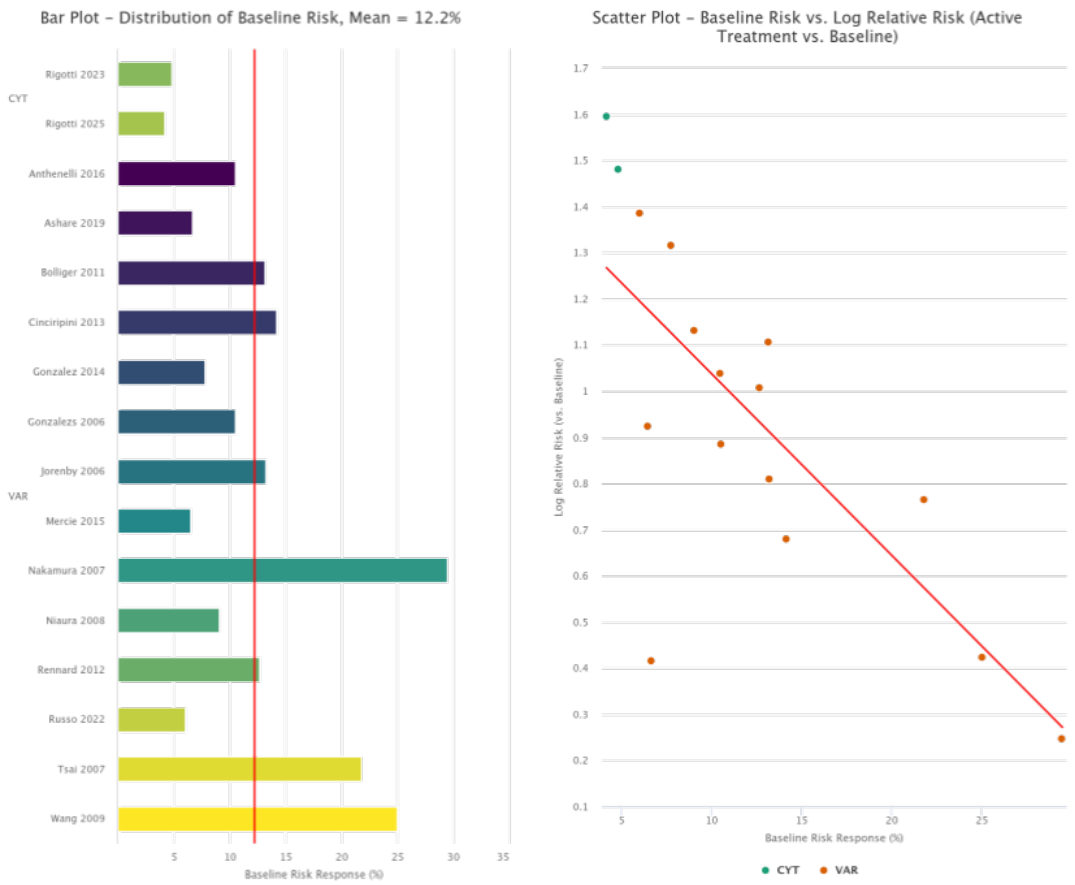


Figure D2.1 provides a visual overview of the strong association between the percentage placebo response (proportion of trial participants in the placebo arm who achieved CAR at weeks 9 to 24) and the relative risk ratio of active treatment against the control group. For example, both cytisinicline trials (ORCA 2 and 3) had the lowest placebo response rates (4.8% and 4.2%) than the average of 12.2% across all trials and subsequently had the highest risk ratios (1.5 and 1.6, respectively). Alternatively, the varenicline trial with the highest placebo response rate (Nakamura 2007, 29.5%) demonstrated the lowest risk ratio of varenicline against placebo.

Table D2.5 provides a quantitative assessment that allowed us to determine whether a baseline risk-adjusted NMA was a better fit than an unadjusted model. We checked whether the regression coefficient had a statistically significant effect on the treatment (meaning the 95% credible interval excluded 0), and if the summary estimate for the between-study standard deviation (SD) and its 95% credible interval decreased. Based on both visual and quantitative assessment of model fit, we decided to use the baseline-risk adjusted NMA for our base-case analysis in our comparison between cytisinicline and varenicline on the outcome of CAR from weeks 9 to 24.

Table D2.5. Assessment of Model Fit, Unadjusted Versus Baseline-Risk Adjusted NMA

Parameter	Unadjusted NMA	Baseline Risk Adjusted NMA	Note
CAR Weeks 9 to 24			
Regression Coefficient (β) (95% CrI)	NA	-0.51 (-0.72 to -0.27)	Statistically significant effect
Heterogeneity SD (95% CrI)	0.24 (0.07 to 0.47)	0.11 (0.01 to 0.27)	Between-study SD reduced
Total Residual Deviance (vs. 32 Data Points)	32.62	34.76	Similar values
Deviance Information Criterion (DIC)	223.26	224.21	Similar values

CrI: credible interval, NMA: network meta-analysis, SD: Standard Deviation

Tables D2.6 and D2.7 demonstrate the impact of adjustment for cross-trial differences. Without adjustment, the CAR at weeks 9 to 24 was significantly higher for the 12-week course of cytisinicline than varenicline. When adjusting for the placebo response, there was no statistically significant difference between the two drugs on abstinence likelihood.

Table D2.6. Risk Ratio for CAR Weeks 9 to 24 (Random Effects Model without Baseline-Risk Adjustment)

CYT 12-Week + Behavioral Support		
1.9 (1.07 to 3.48)	**VAR 12-Week + Behavioral Support**	
4.36 (2.53 to 7.74)	**2.29 (1.91, 2.76)**	**Behavioral Support Alone**

CYT: Cytisinicline, VAR: varenicline

Note: Bolded values indicate statistically significant pairwise comparison.

Table D2.7. Risk Ratio for CAR Weeks 9 to 24 (Random Effects Model with Baseline-Risk Adjustment)

CYT 12-Week + Behavioral Support		
1.1 (0.76 to 1.7)	**VAR 12-Week + Behavioral Support**	
2.71 (1.91 to 4.02)	**2.45 (2.19 to 2.71)**	**Behavioral Support Alone**

CYT: Cytisinicline, VAR: varenicline

Note: Bolded values indicate statistically significant pairwise comparison.

Based on Table D2.8, the baseline-risk adjusted NMA was determined to be a better fit for the abnormal dreams, headache, and nausea outcomes. For insomnia, discontinuation due to adverse events, and serious adverse events outcomes, there was uncertainty about whether the baseline-risk adjusted model provided better fit; the regression coefficients were not statistically significant (95% credible intervals contained 0) and interstudy standard deviations showed minimal changes. Risk ratios for cytisinicline versus varenicline were similar between unadjusted and adjusted models across all uncertain outcomes, with neither model showing statistically significant differences: insomnia (unadjusted RR 1.2 [0.69, 2.06] vs. adjusted RR 1.02 [0.62, 1.72]), discontinuation due to adverse events (unadjusted RR 0.75 [0.28, 1.96] vs. adjusted RR 0.86 [0.36, 2.2]), and serious adverse events (unadjusted RR 1.53 [0.67, 3.66] vs. adjusted RR 1.38 [0.65, 3.06]).

Table D2.8. Assessment of Model Fit, Unadjusted Versus Baseline-Risk Adjusted NMA, by Outcome

Parameter	Unadjusted NMA	Baseline Risk Adjusted NMA	Note
Abnormal Dreams			
Beta (95% CrI)	NA	-0.27 (-0.44 to -0.11)	Statistically significant effect
Heterogeneity SD (95% CrI)	0.31 (0.13 to 0.62)	0.15 (0.01 to 0.44)	Between-study SD reduced
Total Residual Deviance (vs. 36 Data Points)	41.31	42.32	Similar values
Deviance Information Criterion (DIC)	229.5	228.43	Similar values
Headache			
Beta (95% CrI)	NA	-0.22 (-0.39 to -0.04)	Statistically significant effect
Heterogeneity SD (95% CrI)	0.11 (0.01 to 0.27)	0.06 (0 to 0.22)	Between-study SD reduced
Total Residual Deviance (vs. 40 Data Points)	40.25	39.4	Similar values
Deviance Information Criterion (DIC)	258.98	257.08	Similar values
Insomnia			
Beta (95% CrI)	NA	-0.22 (-0.44 to 0.02)	Regression coefficient credible interval contains 0
Heterogeneity SD (95% CrI)	0.2 (0.05 to 0.4)	0.19 (0.03 to 0.38)	No discernible reduction
Total Residual Deviance (vs. 38 Data Points)	38.74	38.31	Similar values
Deviance Information Criterion (DIC)	252.04	252.85	Similar values
Nausea			
Beta (95% CrI)	NA	-0.58(-0.69 to -0.44)	Statistically significant effect
Heterogeneity SD (95% CrI)	0.27(0.15 to 0.45)	0.05(0 to 0.16)	Between-study SD reduced
Total Residual Deviance (vs. 40 Data Points)	42.56	42.1	Similar values
Deviance Information Criterion (DIC)	273.98	267.62	Similar values
Discontinuation Due to AEs			
Beta (95% CrI)	NA	-0.35 (-0.69 to 0)	Regression coefficient credible interval contains 0
Heterogeneity SD (95% CrI)	0.25 (0.02 to 0.64)	0.23 (0.02 to 0.59)	No discernible reduction
Total Residual Deviance (vs. 36 Data Points)	39.49	39.72	Similar values
Deviance Information Criterion (DIC)	198.71	200.37	Similar values

Parameter	Unadjusted NMA	Baseline Risk Adjusted NMA	Note
Serious AEs			
Beta (95% CrI)	NA	-0.29(-0.63 to 0.05)	Regression coefficient credible interval contains 0
Heterogeneity SD (95% CrI)	0.14(0.01 to 0.51)	0.16(0.01 to 0.54)	Increase in value
Total Residual Deviance (vs. 42 Data Points)	44.84	44.98	Similar values
Deviance Information Criterion (DIC)	195.7	197.26	Similar values

AEs: adverse events, CrI: confidence interval, NA: not applicable, NMA: network meta-analysis, SD: standard deviation

NMA Input Data

The inputs abstracted and used in the NMA for each of the seven outcomes are provided in Tables D2.9 through D2.15.

Table D2.9. Input Data for Smoking NMA: Continuous Abstinence Rate Weeks 9-24 (N=16)

Study	12-Week Treatment Arm	Responders	Sample Size
NCT05206370 Rigotti 2025	Cytisinicline	54	264
	Placebo	11	265
NCT04576949 Rigotti 2023	Cytisinicline	57	270
	Placebo	13	271
NCT01387425 Russo 2022	Varenicline	36	150
	Placebo	9	150
NCT01710137 Ashare 2019	Varenicline	9	89
	Placebo	6	90
NCT00918307 Mercie 2018	Varenicline	20	123
	Placebo	8	124
NCT01456936 Anthenelli 2016	Varenicline	256	1005*
	Placebo	106	1009*
NCT01244061 Gonzales 2014	Varenicline	72	249
	Placebo	19	245
NCT00507728 Cinciripini 2013	Varenicline	24	86
	Placebo	15	106
NCT00691483 Rennard 2012	Varenicline	171	493
	Placebo	21	166
NCT00594204 Bolliger 2011	Varenicline	155	390
	Placebo	26	198
NCT00371813 Wang 2009	Varenicline	63	165
	Placebo	42	168
NCT00150228 Niaura 2008	Varenicline	44	157
	Placebo	14	155
NCT00139750 Nakamura 2007	Varenicline	49	130
	Placebo	38	129
NCT00141167 Tsai 2007	Varenicline	59	126
	Placebo	27	124

Study	12-Week Treatment Arm	Responders	Sample Size
NCT00143364 **Jorenby 2006**	Varenicline	102	344
	Placebo	45	341
NCT00141206 **Gonzales 2006**	Varenicline	104	352
	Placebo	36	344

N: number

*Non-psychiatric cohort.

Table D2.10. Input Data for Smoking NMA: Headache (N=20)

Study	12-Week Treatment Arm	Responders	Sample Size
NCT05206370 **Rigotti 2025**	Cytisinicline	22	260
	Placebo	16	262
NCT04576949 **Rigotti 2023**	Cytisinicline	21	270
	Placebo	22	270
NCT01387425 **Russo 2022**	Varenicline	26	150
	Placebo	25	150
NCT02351167 **Chen 2020**	Varenicline	81	274
	Placebo	71	273
NCT00943618 **Cinciripini 2018**	Varenicline	35	166
	Placebo	14	56
NCT01228175 **Littlewood 2017**	Varenicline	31	106
	Placebo	18	87
NCT01456936 **Anthenelli 2016**	Varenicline	116	990*
	Placebo	199	2014[†]
NCT01639560 **Ebbert 2016**	Varenicline	0	45
	Placebo	1	48
NCT01314001 **Lerman 2015**	Varenicline	148	420
	Placebo	169	408
NCT01244061 **Gonzales 2014**	Varenicline	26	249
	Placebo	24	245
NCT00507728 **Cinciripini 2013**	Varenicline	10	86
	Placebo	12	106
NCT00691483 **Rennard 2012**	Varenicline	55	486
	Placebo	20	165
NCT00594204 **Bolliger 2011**	Varenicline	64	390
	Placebo	24	198
NCT00371813 **Wang 2009**	Varenicline	9	165
	Placebo	7	168
NCT00150228 **Niaura 2008**	Varenicline	25	157
	Placebo	20	155
NCT00139750 **Nakamura 2007**	Varenicline	16	156
	Placebo	4	154
NCT00141167 **Tsai 2007**	Varenicline	13	126
	Placebo	16	124
NCT00143364 **Jorenby 2006**	Varenicline	44	343
	Placebo	43	340
NCT00141206 **Gonzales 2006**	Varenicline	54	349
	Placebo	42	344

Study	12-Week Treatment Arm	Responders	Sample Size
NCT00150254 Oncken 2006	Varenicline	29	129
	Placebo	21	121

N: number

*Non-psychiatric cohort.

†Headaches reported across psychiatric and non-psychiatric cohorts for the placebo arm.

Table D2.11. Input Data for Smoking NMA: Nausea (N=20)

Study	12-Week Treatment Arm	Responders	Sample Size
NCT05206370 Rigotti 2025	Cytisinicline	18	260
	Placebo	19	262
NCT04576949 Rigotti 2023	Cytisinicline	15	270
	Placebo	20	270
NCT01387425 Russo 2022	Varenicline	41	150
	Placebo	17	150
NCT02351167 Chen 2020	Varenicline	92	274
	Placebo	59	273
NCT00943618 Cinciripini 2018	Varenicline	64	166
	Placebo	7	56
NCT01228175 Littlewood 2017	Varenicline	52	106
	Placebo	24	87
NCT01456936 Anthenelli 2016	Varenicline	243	990*
	Placebo	63	999*
NCT01639560 Ebbert 2016	Varenicline	10	45
	Placebo	0	48
NCT01314001 Lerman 2015	Varenicline	191	420
	Placebo	111	408
NCT01244061 Gonzales 2014	Varenicline	66	249
	Placebo	22	245
NCT00507728 Cinciripini 2013	Varenicline	23	86
	Placebo	8	106
NCT00691483 Rennard 2012	Varenicline	142	486
	Placebo	15	165
NCT00594204 Bolliger 2011	Varenicline	103	390
	Placebo	16	198
NCT00371813 Wang 2009	Varenicline	48	165
	Placebo	20	168
NCT00150228 Niaura 2008	Varenicline	21	157
	Placebo	8	155
NCT00139750 Nakamura 2007	Varenicline	38	156
	Placebo	12	154
NCT00141167 Tsai 2007	Varenicline	55	126
	Placebo	14	124
NCT00143364 Jorenby 2006	Varenicline	101	343
	Placebo	33	340
NCT00141206 Gonzales 2006	Varenicline	98	349
	Placebo	29	344

Study	12-Week Treatment Arm	Responders	Sample Size
NCT00150254	Varenicline	45	129
Oncken 2006	Placebo	18	121

N: number

*Non-psychiatric cohort

Table D2.12. Input Data for Smoking NMA: Insomnia (N=19)

Study	12-Week Treatment Arm	Responders	Sample Size
NCT05206370	Cytisinicline	31	260
Rigotti 2025	Placebo	20	262
NCT04576949	Cytisinicline	26	270
Rigotti 2023	Placebo	13	270
NCT01387425	Varenicline	29	150
Russo 2022	Placebo	19	150
NCT02351167	Varenicline	55	274
Chen 2020	Placebo	42	273
NCT00943618	Varenicline	60	166
Cinciripini 2018	Placebo	17	56
NCT01228175	Varenicline	35	106
Littlewood 2017	Placebo	15	87
NCT01456936	Varenicline	95	990*
Anthenelli 2016	Placebo	73	999*
NCT01314001	Varenicline	143	420
Lerman 2015	Placebo	133	408
NCT01244061	Varenicline	17	249
Gonzales 2014	Placebo	10	245
NCT00507728	Varenicline	20	86
Cinciripini 2013	Placebo	21	106
NCT00691483	Varenicline	43	486
Rennard 2012	Placebo	6	165
NCT00594204	Varenicline	50	390
Bolliger 2011	Placebo	13	198
NCT00371813	Varenicline	10	165
Wang 2009	Placebo	5	168
NCT00150228	Varenicline	34	157
Niaura 2008	Placebo	17	155
NCT00139750	Varenicline	4	156
Nakamura 2007	Placebo	2	154
NCT00141167	Varenicline	19	126
Tsai 2007	Placebo	17	124
NCT00143364	Varenicline	49	343
Jorenby 2006	Placebo	42	340
NCT00141206	Varenicline	49	349
Gonzales 2006	Placebo	44	344
NCT00150254	Varenicline	48	129
Oncken 2006	Placebo	14	121

N: number

*Non-psychiatric cohort

Table D2.13. Input Data for Smoking NMA: Abnormal Dreams (N=18)

Study	12-Week Treatment Arm	Responders	Sample Size
NCT05206370 Rigotti 2025	Cytisinicline	20	260
	Placebo	15	262
NCT04576949 Rigotti 2023	Cytisinicline	21	270
	Placebo	8	270
NCT01387425 Russo 2022	Varenicline	19	150
	Placebo	5	150
NCT02351167 Chen 2020	Varenicline	100	274
	Placebo	60	273
NCT00943618 Cinciripini 2018	Varenicline	57	166
	Placebo	6	56
NCT01228175 Littlewood 2017	Varenicline	50	106
	Placebo	25	87
NCT01456936 Anthenelli 2016	Varenicline	83	990*
	Placebo	39	999*
NCT01314001 Lerman 2015	Varenicline	186	420
	Placebo	132	408
NCT01244061 Gonzales 2014	Varenicline	36	249
	Placebo	8	245
NCT00507728 Cinciripini 2013	Varenicline	13	86
	Placebo	11	106
NCT00691483 Rennard 2012	Varenicline	61	486
	Placebo	5	165
NCT00594204 Bolliger 2011	Varenicline	8	390
	Placebo	0	198
NCT00371813 Wang 2009	Varenicline	6	165
	Placebo	5	168
NCT00150228 Niaura 2008	Varenicline	7	157
	Placebo	6	155
NCT00141167 Tsai 2007	Varenicline	7	126
	Placebo	1	124
NCT00143364 Jorenby 2006	Varenicline	45	343
	Placebo	12	340
NCT00141206 Gonzales 2006	Varenicline	36	349
	Placebo	19	344
NCT00150254 Oncken 2006	Varenicline	25	129
	Placebo	6	121

N: number

*Non-psychiatric cohort.

Table D2.14. Input Data for Smoking NMA: Discontinuation Due to Adverse Event (N=18)

Study	12-Week Treatment Arm	Responders	Sample Size
NCT05206370 Rigotti 2025	Cytisinicline	5	260
	Placebo	3	262
NCT04576949 Rigotti 2023	Cytisinicline	10	270
	Placebo	4	270
NCT01387425 Russo 2022	Varenicline	6	150
	Placebo	5	150
NCT00918307 Mercie 2018	Varenicline	11	123
	Placebo	8	125
NCT00943618 Cinciripini 2018	Varenicline	13	166
	Placebo	1	56
NCT01456936 Anthenelli 2016	Varenicline	57	990*
	Placebo	29	999*
NCT01639560 Ebbert 2016	Varenicline	0	45
	Placebo	2	48
NCT01244061 Gonzales 2014	Varenicline	18	249
	Placebo	7	245
NCT00507728 Cinciripini 2013	Varenicline	1	86
	Placebo	1	106
NCT00691483 Rennard 2012	Varenicline	24	486
	Placebo	13	165
NCT00594204 Bolliger 2011	Varenicline	16	390
	Placebo	3	198
NCT00371813 Wang 2009	Varenicline	3	165
	Placebo	3	168
NCT00150228 Niaura 2008	Varenicline	11	157
	Placebo	7	155
NCT00139750 Nakamura 2007	Varenicline	5	156
	Placebo	3	154
NCT00141167 Tsai 2007	Varenicline	8	126
	Placebo	1	124
NCT00143364 Jorenby 2006	Varenicline	36	343
	Placebo	25	340
NCT00141206 Gonzales 2006	Varenicline	30	349
	Placebo	31	344
NCT00150254 Oncken 2006	Varenicline	28	129
	Placebo	21	121

N: number

*Non-psychiatric cohort

Table D2.15. Input Data for Smoking NMA: Serious Adverse Events (N=22)

Study	12-Week Treatment Arm	Responders	Sample Size
NCT05206370 Rigotti 2025	Cytisinicline	8	260
	Placebo	8	262
NCT04576949 Rigotti 2023	Cytisinicline	8	270
	Placebo	3	270
NCT01387425 Russo 2022	Varenicline	1	105
	Placebo	2	96
NCT02351167 Chen 2020	Varenicline	17	274
	Placebo	27	273
NCT01710137 Ashare 2019	Varenicline	5	89
	Placebo	3	90
NCT00918307 Mercie 2018	Varenicline	12	102
	Placebo	12	111
NCT00943618 Cinciripini 2018	Varenicline	4	166
	Placebo	1	56
NCT01228175 Littlewood 2017	Varenicline	2	106
	Placebo	0	87
NCT01456936 Anthenelli 2016	Varenicline	16	990*
	Placebo	16	999*
NCT01639560 Ebbert 2016	Varenicline	0	45
	Placebo	0	48
NCT01314001 Lerman 2015	Varenicline	11	420
	Placebo	16	408
NCT01244061 Gonzales 2014	Varenicline	7	249
	Placebo	4	245
NCT00507728 Cinciripini 2013	Varenicline	2	86
	Placebo	2	106
NCT00691483 Rennard 2012	Varenicline	6	486
	Placebo	1	165
NCT00594204 Bolliger 2011	Varenicline	11	390
	Placebo	2	198
NCT00371813 Wang 2009	Varenicline	0	165
	Placebo	2	168
NCT00150228 Niaura 2008	Varenicline	3	157
	Placebo	0	155
NCT00139750 Nakamura 2007	Varenicline	3	156
	Placebo	3	154
NCT00141167 Tsai 2007	Varenicline	3	126
	Placebo	3	124
NCT00143364 & NCT00141206 Jorenby & Gonzales 2006	Varenicline	9	692
	Placebo	12	684
NCT00150254 Oncken 2006	Varenicline	4	259
	Placebo	2	121

N: number

*Non-psychiatric cohort

Vaping Cessation

Similar to our aims in Question 2, we conducted an exploratory indirect treatment comparison between cytisinicline and varenicline in individuals looking to quit use of electronic cigarettes/vaping. We identified three similar studies which treated patients with either a 12-week course of cytisinicline or varenicline as-addons to behavioral support versus behavioral support alone. Supplement Table D3.4 outlines some shared baseline characteristics. The average age of trial participants varied between trials; with the average age of participants in the Evins 2025 trial being 21 versus approximately 52 in the VAREVAPE (Caponnetto 2023) trial. Measures of baseline electronic cigarette dependence were similar across study arms in the network, ranging from an average of 11.7 to 14.9 on a 20-point scale.

Table D2.16 outlines the values as inputs for the seven-day point prevalence at week 12 vaping abstinence NMA. Our initial outcome of interest, continuous abstinence rate at weeks 9 to 24 was not possible due to data availability across the three trials. A comparative analysis of harms between cytisinicline, varenicline, and control among vaping users were not possible due to differences in measurement and data availability.

Table D2.16. Input Data for Vaping NMA: Seven-Day Point-Prevalence (N=3)

Study		NCT05431387 Rigotti 2024		NCT05367492 Evins 2025		VAREVAPE Caponnetto 2023	
12-Week Treatment Arm		Cytisinicline	Placebo	Varenicline	Placebo	Varenicline	Placebo
N		107	53	88	87	70	70
Seven-Day Point Prevalence, Responders	Week 12	*41*	*12*	60	22	28	14

N: number

Note: Italicized indicates data was digitized.

This NMA used a random-effects model to account for between-study variability in treatment effects and found no statistically significant difference between cytisinicline and varenicline or behavioral support alone on the outcome of seven-day point prevalence (Table D2.17). Applying a fixed-effect model altered the point estimate between varenicline and placebo to be statistically significant.

Table D2.17. NMA Results- Seven-Day Point Prevalence at Week 12- Risk Ratio (95% Credible Interval) Random Effects Model

CYT 12-Week + Behavioral Support		
0.72 (0.06, 8.78)	VAR 12-Week + Behavioral Support	
1.65 (0.22, 12.78)	2.3 (0.55, 9.54)	Behavioral Support Alone

CYT: Cytisinicline, VAR: Varenicline

Table D2.18. NMA Results- Seven-Day Point Prevalence at Week 12- Risk Ratio (95% Credible Interval) Fixed Effect Model

CYT 12-Week + Behavioral Support		
0.69 (0.38, 1.33)	VAR 12-Week + Behavioral Support	
1.62 (0.98, 2.92)	**2.36 (1.77, 3.28)**	**Behavioral Support Alone**

CYT: Cytisinicline, VAR: Varenicline

NMA Limitations

- To maintain similarity between trials in our NMA, we excluded trials of smokers with major comorbidities such as psychiatric or substance abuse. However, we note that Americans with mental illness have higher smoking rates and consume more cigarettes than the general population.[79] It's important to know whether cytisinicline can assist smoking cessation in vulnerable and underserved populations.
- In clinical trials, participants received behavioral support that is likely to be of greater intensity than what is available outside of an experimental setting. It is unknown what synergistic effect behavioral support may have with cytisinicline. This may be more relevant in some countries like Canada where cytisinicline is available over the counter and unlikely to be paired with behavioral support.

D3. Evidence Tables

Table D3.1. Study Design

Trial (NCT)	Study Design	Arms & Dosing Regimen	Inclusion / Exclusion Criteria	Primary Outcomes
ORCA-2 (NCT04576949)	Phase III randomized, Double-Blind, Placebo-Controlled, Clinic-based N=810	All arms received oral tablets TID with behavioral support. **Placebo**: placebo for 12 weeks (n=271). **Cytisinicline/Placebo:** cytisinicline for six weeks, then placebo for six weeks (n=269). **Cytisinicline:** cytisinicline for 12 weeks (n=270).	**Inclusion**: • Adults (≥18 years) who are current daily cigarette smokers (≥10 cigarettes/day for the past week) intending to quit. • Expired air carbon monoxide (CO) ≥10 ppm. • ≥1 prior unsuccessful quit attempt, with or without therapeutic support. • Willing to set a quit date and engage in behavioral support throughout study. **Exclusion**: • Prior cytisinicline use or known hypersensitivity to it or its excipients. • Positive urine drug screen within 28 days prior to first dose. • BMI <18.5 kg/m^2 (underweight) or ≥35 kg/m^2 (≥Class 2 obesity). • Recent history of acute myocardial infarction, unstable angina, stroke, cerebrovascular incident or hospitalization for congestive heart failure.	Proportion of participants with smoking abstinence during the last four weeks of six-week (weeks 3-6) and 12-week (weeks 9-12) cytisinicline treatment vs. placebo.
ORCA-3 (NCT05206370)	Phase III randomized, Double-Blind, Placebo-Controlled, Clinic-based N=792	All arms received oral tablets TID with behavioral support. **Placebo**: placebo for 12 weeks (n=262). **Cytisinicline/Placebo:** cytisinicline for six weeks, then placebo for six weeks (n=263). **Cytisinicline:** cytisinicline for 12 weeks (n=260).		

Trial (NCT)	Study Design	Arms & Dosing Regimen	Inclusion / Exclusion Criteria	Primary Outcomes
			• Current uncontrolled hypertension, suicidal ideation/risk, moderate to severe depression symptoms, and/or renal/hepatic impairment. • Diagnosis of schizophrenia, bipolar disorder, or active psychosis. • Pregnant or breast-feeding women. • Recent or planned use of bupropion, varenicline, nortriptyline, or any NRT. • Use of non-cigarette, noncombustible nicotine products or marijuana within two weeks prior to or during the study.	
ORCA-V1 (NCT05431387)	Phase II, Randomized, Double-Blind, Placebo-Controlled, Clinic-based N=160	All arms received oral tablets TID with behavioral support. **Placebo:** placebo for 12 weeks (n=53) **Cytisinicline:** cytisinicline for 12 weeks (n=107)	**Inclusion** • Adults (≥18 years) who are current daily nicotine-containing electronic cigarette users. • Positive (≥30 ng/mL) saliva cotinine test result. • Willing to set a quit date and engage in behavioral support throughout study. **Exclusion** • Current or recent (past four weeks) smoking of any combustible cigarettes, other combustible or non-combustible tobacco products.	Proportion of participants with vaping abstinence during weeks 9 to 12

Trial (NCT)	Study Design	Arms & Dosing Regimen	Inclusion / Exclusion Criteria	Primary Outcomes
			• Expired CO levels ≥ 10 ppm. • Known hypersensitivity to cytisinicline or any of its excipients. • Positive urine drug screen within 28 days prior to first dose. • Recent history of acute myocardial infarction, unstable angina, stroke, cerebrovascular incident or hospitalization for congestive heart failure. • Current uncontrolled hypertension, suicidal ideation/risk, and/or renal/hepatic impairment. • Diagnosis of schizophrenia, bipolar disorder, or active psychosis. • Pregnant or breast-feeding women. • Recent or planned use of bupropion, varenicline, nortriptyline, or any NRT. • Planned use of combustible cigarettes or other nicotine-containing, non-vaping products.	

BMI: body mass index, kg/m^2: kilograms per square meter, N: number, ng/mL: nanograms per milliliters, NRT: nicotine replacement therapy, ppm: parts per million, TID: three times daily

Table D3.2. Baseline Characteristics of Key Studies for Cytisinicline[11,12]

Trial			ORCA-2		ORCA-3	
Arms*			12-Week Cytisinicline	12-Week Placebo	12-Week Cytisinicline	12-Week Placebo
N			270	271	264	265
Age, Mean Years (SD)			53.3 (11.6)	52.0 (12.0)	52 (12.3)	51 (11.4)
Female sex, n (%)			135 (50.0)	159 (58.7)	151 (57.2)	119 (44.9)
Race, n (%)	Black or African American		48 (17.8)	42 (15.5)	50 (18.9)	51 (19.2)
	White		216 (80.0)	221 (81.5)	205 (77.7)	210 (79.2)
	Other†		*6 (2.2)*	*8 (3.0)*	*9 (3.4)*	*4 (1.6)*
Hispanic Ethnicity, n (%)			23 (8.5)	19 (7.0)	13 (4.9)	17 (6.4)
Tobacco Use, Mean (SD)	Duration of smoking, years		37.0 (12.9)	36.5 (12.6)	34.8 (13.6)	34.5 (12.4)
	Cigarettes per day‡		19.4 (7.2)	19.4 (7.7)	20.0 (7.4)	20.0 (7.1)
	FTND score§		5.6 (1.9) [n=269]	5.6 (1.7)	5.6 (1.9)	5.6 (1.9)
Quitting History	Prior quit attempts, median (IQR)		4 (2-6)	4 (2-6)	4.0 (2-6.5)	4.0 (3-6)
	Prior cessation medication used, n (%)	NRT lozenges	174 (64.4)#	171 (63.1)#	26 (9.8)	30 (11.3)
		NRT gum			107 (40.5)	113 (42.6)
		NRT patch			132 (50.0)	160 (60.4)
		Varenicline	127 (47.0)	114 (42.1)	102 (38.6)	110 (41.5)
		Bupropion	57 (21.1)	56 (20.7)	52 (19.7)	67 (25.3)
	Prior cessation behavioral support used, n (%)¤		30 (11.1)	23 (8.5)	NR	NR

FTND: Fagerström Test for Nicotine Dependence, IQR: interquartile range, N: number, NR: not reported, NRT: nicotine replacement therapy, SD: standard deviation

Note: Italicized results in the table were calculated from data reported in the trials.

*All arms were administered with behavioral support.

†Includes Asian, American Indian or Alaska native, native Hawaiian or other Pacific Islander, and any race or ethnicity not listed.

‡ORCA-2 for 7 consecutive days. For ORCA-3, for 30 days.

§Fagerström 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.

#Includes counseling support received in person, by phone, or via web.

¤May include nasal sprays and inhalers.

Table D3.3. Key Tolerability and Safety Events of Cytisinicline 3 mg TID + Behavioral Support Versus Placebo/Behavioral Support Alone (Meta-Analysis)

		Meta-Analysis (Fixed Effects)	
		Overall Effect Estimates, Risk Ratio (95% CI)	**Absolute Risk Difference (95% CI)**
Most Frequent TEAEs	**Headache**	1.14 (0.75, 1.73)	0.01 (-0.02, 0.04)
	Nausea	0.85 (0.54, 1.33)	-0.01 (-0.04, 0.02)
	Insomnia	**1.73 (1.15, 2.62)**	**0.05 (0.01, 0.08)**
	Abnormal Dreams	**1.79 (1.09, 2.94)**	**0.03 (0.01, 0.06)**
Discontinuation due to AEs		2.15 (0.88, 5.23)	0.02 (-0.00, 0.03)
Serious AEs		1.46 (0.68, 3.12)	0.01 (-0.01, 0.03)

AEs: adverse events, CI: confidence interval, CrI: credible interval, n: number, RR: risk ratio, TEAEs: treatment-emergent adverse events

*All arms were administered with behavioral support.

Table D3.4. Baseline Characteristics of Vaping Cessation Trials[17-19]

Trial Name		**ORCA-V1**		**ViVA**		**VAREVAPE**	
Arms*		**12-Week Cytisinicline**	**12-Week Placebo**	**12-Week Varenicline**	**12-Week Placebo**	**12-Week Varenicline**	**12-Week Placebo**
N		**107**	**53**	**88**	**87**	**70**	**70**
Age, Mean Years (SD)		33.6 (11.2)	33.5 (10.9)	21.6 (2)	21.4 (2.1)	53.8 (9.7)	51.3 (8.4)
Female Sex, n (%)		54 (50.5)	29 (54.7)	46 (53)	47 (54)	34 (48.6)	37 (52.9)
Race, n (%)	**Asian**	3 (2.8)	3 (5.7)	13 (15)	17 (20)	NR	NR
	Black	9 (8.4)	5 (9.4)	5 (6)	7 (8)	NR	NR
	White	92 (86.0)	43 (81.1)	56 (64)	47 (54)	NR	NR
Electronic Cigarette Dependence inventory, mean (SD)†		12.9 (4.1)	13.5 (3.9)	12.5 (3.8)	13.7 (4)	11.7 (6.2)	14.9 (7.3)

n: number, NR: not reported, SD: standard deviation

*All arms were administered with behavioral support.

†As measured by the Penn State Electronic Cigarette Dependence Index (ECDI), a 10-item scale with a range of scores from 0 to 20. Higher scores indicate greater dependence.[62]

D4. Ongoing Studies

Table D4.1. Ongoing Studies

Title, NCT, & Trial Sponsor	Study Design	Arms	Inclusion Criteria & Patient Population	Primary Outcomes	Estimated Completion Date
ORCA-OL **NCT06435221** **Achieve Life Sciences**	Phase III open-label study assessing long-term exposure with cytisinicline for smoking and electronic cigarette cessation. N=650	Cytisinicline 3 mg TID for 52 weeks in addition to behavioral support.	• Prior participation in ORCA-2, ORCA-3 or ORCA-V1. • Current daily cigarette smokers and/or daily nicotine-containing electronic cigarette users, aged ≥18 years. • Subjects must have expired carbon monoxide (CO) ≥10 ppm if self-reporting as smokers, or ≥30 ng/mL cotinine if self-reporting as electronic cigarette users. • Subjects are willing to initiate study treatment on the day after enrollment, set a quit date within 14 days of starting treatment, and participate in the behavioral support provided throughout the study.	Incidence rate of treatment emergent serious adverse events (SAEs).	December 2025
ORCA-V2 **Achieve Life Sciences**	Phase III study assessing the efficacy and safety of cytisinicline for nicotine electronic cigarette cessation. N=800	Cytisinicline 3 mg TID for 52 weeks in addition to behavioral support.	• Current nicotine-containing electronic cigarette users, aged ≥18 years. • Subjects have failed at least one previous attempt to stop vaping nicotine. • Subjects do not smoke cigarettes.	Weekly vaping abstinence with biochemical confirmation from weeks 9 to 12.	Unknown

Source: www.ClinicalTrials.gov and https://achievelifesciences.com/

Mg: milligrams, N: number, ng/mL: nanograms per milligrams, OL: open-label, ppm: parts per million, TID: three times daily

Note: studies listed on site include both clinical trials and observational studies

D5. Previous Systematic Reviews and Technology Assessments

We reviewed several systematic reviews of pharmacotherapies for smoking cessation outlined below.

Cochrane Review 2023: Pharmacological and electronic cigarette interventions for smoking cessation in adults: component network meta-analyses

The 2023 Cochrane review was the foundation for our evidence base in comparing cytisinicline against combination NRT, electronic cigarettes, and bupropion. These comparisons are featured in the clinical evidence section of the report across Research Questions 3 to 6.

The review found high-certainty evidence that electronic cigarettes (OR 2.37; 95% CrI: 1.73 to 3.24; 16 RCTs, 3,828 participants), varenicline (OR 2.33; 95% CrI: 2.02 to 2.68; 67 RCTs, 16,430 participants), and cytisinicline (OR 2.21; 95% CrI: 1.66 to 2.97; 7 RCTs, 3,848 participants) were associated with higher quit rates than control. This translates to about seven to eight additional quitters per 100. These were more effective than other interventions except combination NRT (patch plus fast-acting NRT), which had a slightly lower but overlapping effect (OR 1.93; 95% CrI: 1.61 to 2.34). Bupropion also showed high-certainty evidence of effectiveness (OR 1.43; 95% CrI: 1.26 to 1.62; 71 RCTs, 14,759 participants), resulting in about three additional quitters per 100.

National Institute for Health and Care Excellence 2025: Evidence review Q for cytisinicline for smoking cessation

This assessment built upon the 2023 Cochrane review by incorporating four new RCTs involving cytisinicline.

A meta-analysis of five RCTs (including the six-week cytisinicline treatment arm of ORCA-2) involving 4,755 participants calculated a RR of 1.82 (95% CI: 1.18 to 2.81) for smoking abstinence at the longest follow-up (6 months or longer) when comparing cytisinicline to placebo. The certainty of this evidence was rated as moderate according to GRADE. For serious adverse events, based on three RCTs with 3,553 participants, the RR was 1.28 (95% CI: 0.90 to 1.82), with moderate certainty indicating no clear difference between cytisinicline and placebo. However, there was an increased risk of insomnia (RR 1.83; 95% CI: 1.12 to 2.98) and abnormal dreams (RR 2.26; 95% CI: 1.16 to 4.41) associated with cytisinicline.

Compared to varenicline, cytisinicline had a lower treatment effect on smoking abstinence (RR 0.92; 95% CI: 0.67 to 1.28) based on very low-certainty evidence from three RCTs, two with high risk of bias. Cytisinicline showed lower risks of serious adverse events (RR 0.67; 95% CI: 0.46 to 0.96), nausea (RR 0.41; 95% CI: 0.33 to 0.50), abnormal dreams (RR 0.59; 95% CI: 0.23 to 1.49), insomnia (RR 0.79; 95% CI 0.44 to 1.39), and similar risk of headache (RR 1.04; 95% CI 0.80 to 1.35).

D6. Heterogeneity and Subgroups

Table D6.1. Continuous Abstinence at End of Treatment: Subgroup Analysis of ORCA-2[11]

Subgroup		12-Week Cytisinicline (N=270)	12-Week Placebo (N=271)	Effect Modifier, p-Value
<65 Years Old	n	232	242	0.837
	Effect OR (95% CI)	6.57 (3.74,11.57)		
≥65 Years Old	n	38	29	
	Effect OR (95% CI)	5.50 (1.11,27.29)		
Female	n	135	159	0.715
	Effect OR (95% CI)	7.21 (3.63,14.31)		
Male	n	135	112	
	Effect OR (95% CI)	5.88 (2.50,13.80)		
≤20 Cigarettes per Day	n	93	94	0.321
	Effect OR (95% CI)	10.20 (3.41,30.50)		
>20 Cigarettes per Day	n	177	177	
	Effect OR (95% CI)	5.40 (2.92,10.00)		
≤4 Prior Quits	n	118	116	0.380
	Effect OR (95% CI)	5.08 (2.45,10.54)		
>4 Prior Quits	n	152	155	
	Effect OR (95% CI)	8.22 (3.72,18.16)		

CI: confidence interval, n: number, OR: odds ratio

Table D6.2. Continuous Vaping Cessation at End of Treatment: Subgroup Analysis of ORCA-V1[17]

Subgroup			12-Week Cytisinicline (N=107)	Placebo (N=53)	Effect Modifier, p-Value
Age	**<24.5 Years Old**	n	28	12	0.5233
		Effect OR (95% CI)	1.667 (0.288, 9.654)		
	24.5–31 Years Old	n	22	13	
		Effect OR (95% CI)	10.000 (1.082, 92.402)		
	31–40 Years Old	n	27	15	
		Effect OR (95% CI)	2.737 (0.492, 15.226)		
	≥40 years old	n	30	13	
		Effect OR (95% CI)	1.429 (0.312, 6.533)		
Sex	**Female**	n	54	29	0.5184
		Effect OR (95% CI)	2.021 (0.649, 6.291)		
	Male	n	53	24	
		Effect OR (95% CI)	3.600 (0.936, 13.846)		
Race	**Other**	n	15	10	0.8325
		Effect OR (95% CI)	3.273 (0.303, 35.369)		
	White	n	92	43	
		Effect OR (95% CI)	2.488 (0.985, 6.286)		
>100 Lifetime Cigarettes	**No**	n	30	15	0.8340
		Effect OR (95% CI)	2.316 (0.528, 10.157)		
	Yes	n	77	38	
		Effect OR (95% CI)	2.811 (0.966, 8.179)		

Subgroup			12-Week Cytisinicline (N=107)	Placebo (N=53)	Effect Modifier, p-Value
Age Started Vaping	**<22 Years Old**	n	36	17	0.3798
		Effect OR (95% CI)	2.053 (0.484, 8.717)		
	22–33 Years Old	n	31	22	
		Effect OR (95% CI)	6.316 (1.230, 32.434)		
	≥33 Years Old	n	40	14	
		Effect OR (95% CI)	1.391 (0.322, 6.016)		
Tobacco Flavored	**No**	n	96	49	0.5108
		Effect OR (95% CI)	2.862 (1.147, 7.141)		
	Yes	n	11	4	
		Effect OR (95% CI)	1.125 (0.080, 15.828)		
ECDI Baseline Score	**<12**	n	38	13	0.4576
		Effect OR (95% CI)	1.313 (0.337, 5.116)		
	12–15	n	30	20	
		Effect OR (95% CI)	2.833 (0.662, 12.135)		
	≥15	n	39	19	
		Effect OR (95% CI)	6.207 (0.719, 53.560)		

CI: confidence interval, ECDI: Electronic Cigarette Dependence Inventory, n: number, OR: odds ratio

E. Long-Term Cost-Effectiveness: Supplemental Information

E1. Detailed Methods

Table E1.1. Impact Inventory

Sector	Type of Impact (Add Additional Domains, as Relevant)	Included in This Analysis from […] Perspective?		Notes on Sources (if Quantified), Likely Magnitude & Impact (if Not)
		Health Care Sector	Societal	
Formal Health Care Sector				
Health Outcomes	Longevity effects	X	X	
	Health-related quality of life effects	X	X	
	Adverse events	X	X	
Medical Costs	Paid by third-party payers	X	X	
	Paid by patients out-of-pocket	☐	X	
	Future related medical costs	X	X	
	Future unrelated medical costs	X	X	
Informal Health Care Sector				
Health-Related Costs	Patient time costs	NA	☐	
	Unpaid caregiver-time costs	NA	☐	
	Transportation costs	NA	☐	
Non-Health Care Sector				
Productivity	Labor market earnings lost	NA	☐	
	Cost of unpaid lost productivity due to illness	NA	☐	
	Cost of uncompensated household production	NA	☐	
Consumption	Future consumption unrelated to health	NA	☐	
Social Services	Cost of social services as part of intervention	NA	☐	
Legal/Criminal Justice	Number of crimes related to intervention	NA	☐	
	Cost of crimes related to intervention	NA	☐	
Education	Impact of intervention on educational achievement of population	NA	☐	
Housing	Cost of home improvements, remediation	NA	☐	
Environment	Production of toxic waste pollution by intervention	NA	☐	
Other	Other impacts (if relevant)	NA	☐	

NA: not applicable

Adapted from Sanders et al[80]

Description of evLY Calculations

The equal value life year (evLY) considers any extension of life at the same "weight" no matter what treatment is being evaluated or what population is being modeled. Below are the stepwise calculations used to calculate the evLY.

1. First, we attribute a utility of 0.851, the age- and sex-adjusted utility of the general population in the US that are considered healthy.[81]
2. We calculate the evLY for each model cycle.
3. Within a model cycle, if using the intervention results in additional life years versus the primary comparator, we multiply the general population utility of 0.851 with the additional life years gained (ΔLY gained) within the cycle.
4. The life years shared between the intervention and the comparator use the conventional utility estimate for those life years within the cycle.
5. The total evLY for a cycle is calculated by summing steps three and four.
6. The evLY for the comparator arm is equivalent to the QALY for each model cycle.
7. The total evLYs are then calculated as the sum of evLYs across all model cycles over the time horizon.

Finally, the evLYs gained is the incremental difference in evLYs between the intervention and the comparator arm.

Target Population

The population of focus for the economic evaluation was based on patients from the ORCA-2 and ORCA-3 trials, which assessed 12 weeks of treatment with cytisinicline for smoking cessation compared to placebo. Baseline characteristics in Table 4.2. were calculated as a weighted average across both clinical trials.

Table E1.2. Base Case Model Cohort Characteristics

	Value (Weighted Average)
Mean Age (SD)	52.1 (11.8)
Percent Male	44.8
Daily Average Cigarettes Smoked (SD)	19.7 (7.4)
Source	ORCA-2 & ORCA-3[11,12]

SD: standard deviation

Treatment Strategies

The list of interventions was developed with input from patient organizations, clinicians, manufacturers, and payers on which treatments to include. The full list of interventions is as follows:

- 12 weeks of cytisinicline with behavioral support

Comparators

The comparators for this intervention were:

- 12 weeks of varenicline with behavioral support
- Behavioral support alone

E2. Model Inputs and Assumptions

Model Inputs

Clinical Inputs

Clinical Probabilities of Smoking-Related Conditions.

The probabilities of transitioning between smoking-related health states were stratified by smoking status (current vs. former) (Table 4.3). When available, estimates derived from studies conducted in US populations were prioritized. The age-specific incidence of COPD in current and former smokers were obtained from the Rotterdam Study, a European prospective cohort study of 14,619 individuals, in which COPD was defined based on a post-bronchodilator FEV1/FVC ratio <0.70, consistent with GOLD guidelines.[28] Lung cancer incidence was derived from an analysis of the Framingham Heart Study, which included 9,907 US participants and determined lung cancer diagnoses through medical record reviews, pathology reports, and laboratory findings.[29] Incidence of CVD events for current and former smokers were informed by a US-based study of 6,814 participants, where CVD outcomes, including hospitalizations, outpatient diagnoses of coronary heart disease and cerebrovascular disease, and deaths, were collected via interview and adjudicated by physicians.[30]

We applied hazard ratios (HRs) to account for the elevated risk of a CVD event among patients with COPD and lung cancer (Table 4.4). For patients with COPD, we used estimates from a UK-based study of 29,870 individuals with COPD, in which CVD was defined as angina, MI, heart failure, peripheral vascular disease, and aortic aneurysm.[31] Stroke was defined separately to include subarachnoid hemorrhage, intracranial hemorrhage, and transient ischemic attack. Given our use of a composite CVD event definition that includes both CVD and stroke, we calculated a composite hazard ratio by taking a weighted geometric mean of the HRs for CVD and stroke, assuming a 50/50 distribution. For patients with lung cancer, we used estimates from a large prospective study of 478,756 individuals without CVD at baseline, which assessed the risk of incident CVD events by lung cancer status.[32] In this study, CVD events were defined as nonfatal coronary heart disease (CHD), heart failure (HF), and stroke.

Mortality

To model mortality, we followed a prior published approach of producing a revised life table that reflects the mortality experience of never smokers by starting from the 2023 United States life table and removing the smoking attributable portion of mortality.[82,83] Then, we used a mixture approach based on contemporary smoking prevalence and all cause relative risks (RR) for current and former smokers versus never smokers, to re-estimate the never smoker baseline mortality.[35,84,85] For each age, we converted the population probability of death to a one year hazard, adjusted this by dividing through a mixture factor that incorporates the observed shares of current, former, and never smokers with their relative risks, and then converted the adjusted hazard back to the probability of death for a never smoker.[86,87] From this revised life table of never smokers, we applied the condition-specific RR's outlined in Table 4.6 of the Main Report.

To estimate RR's of death for current and former smokers with no comorbidities, we used death counts for smoking-related conditions (i.e., COPD, lung cancer, and CVD) and all-cause death, and their respective RR's compared to never smokers.[35] For each cause we divided the number of deaths in the smoking group by the cause specific relative risk to obtain the implied number of deaths for never smokers for that specific cause. These implied never smoker deaths were then summed across the modeled causes. We then divided the total all cause deaths by the all-cause relative risk to obtain the never smoker baseline number of deaths for all causes combined. The difference between this all-cause baseline and the summed cause-specific baseline deaths represented the residual category of deaths not attributed to modeled conditions. The residual relative risk for each smoking group was calculated as the ratio of observed residual deaths (i.e., all-cause deaths minus modeled cause deaths) to this residual baseline among never smokers. We implemented this approach for former and for current smokers.

Utilities

Caregiver Disutilities

Caregiver disutilities for smoking-related conditions were included in the modified societal perspective analysis. For COPD, lung cancer, and CVD health states, we assumed one caregiver per patient and the disutility was applied for the duration of the model. There is limited evidence on caregiver disutility specific to COPD. Given that caregivers of patients with COPD provide an estimated 20 hours of care per week, we used data from a study reporting an average EQ-5D utility of 0.79 among primary caregivers providing at least this level of care.[88,89] Assuming a baseline utility of 0.851 for a healthy individual,[40] we applied a disutility of 0.06 to reflect the quality-of-life impact on caregivers of patients with COPD. There is also limited evidence on caregiver disutility specific to CVD. To provide a conservative estimate, we used data from a heart failure study as a proxy. Caregivers of patients with New York Heart Association Class II-IV had an average EQ-5D-5L utility of 0.75.[90] Using the same baseline utility of 0.851 for a healthy individual, we applied a disutility of 0.10 to reflect the quality-of-life impact on caregivers of patients with CVD. For lung cancer, we used a caregiver disutility of 0.30 based on a study of US participants that used the standard gamble method to estimate disutility among caregivers of general cancer patients.[91]

For caregivers of patients with multiple conditions, we used a multiplicative approach to calculate the total disutility. For example. A caregiver of a patient who has COPD and CVD had a disutility of 0.06 + 0.10 – (0.06*0.10)/0.851=0.153.

Economic Inputs

Administration and Monitoring Costs

The inputs in Table E2.1 were used to model drug utilization and associated costs.

Table E2.1. Treatment Regimen Recommended Dosage

Generic Name	Cytisinicline*	Varenicline*
Brand Name	NA	Chantix®
Manufacturer	Achieve Life Sciences	Pfizer
Route of Administration	Oral	Oral
Dosing	3 mg three times daily for 12 weeks (84 days)	0.5 mg daily (days 1-3), 0.5 mg twice daily (days 4-7), 1 mg twice daily (days 8-84)

NA: not available

*Each treatment is in addition to weekly behavioral support therapy for 12 weeks

Health Care Utilization Costs

For patients who experience a CVD event, acute care costs were applied based on a study that estimated nationally representative hospitalization costs for CVD events using the National Inpatient Sample.[49] Health care costs associated post-CVD event were obtained from studies that estimated direct medical costs using nationally representative data from Medical Expenditure Panel Survey (MEPS).[50,51] COPD-related health state costs were estimated from an administrative claims-based database of COPD patients and the overall group were used instead of COPD Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage specific estimates. The same study was used to estimate unrelated COPD costs by subtracting COPD-related costs from all-cause costs. A similar approach was taken with lung cancer for lung cancer-related and unrelated costs from a study that assessed non-small cell lung cancer patients using Surveillance, Epidemiology, and End Results (SEER)-Medicare data. For unrelated costs without any comorbidities and CVD health states, we used a study that assessed age-specific average health care costs among US adults using MEPS data.[48]

E3. Results

Table E3.1. show the results for smoke-free years, CVD events, COPD cases, and lung cancer cases for each of the smoking cessation interventions. CVD events were similar across the three interventions as the estimates that we used did not show a large difference between former (0.29% per 3 months) and current smokers (0.31% per three months). Lung cancer cases were also similar across the three interventions as the risk between current (0.05% per three months) and former smokers (0.04% per three months) was small. COPD cases showed the largest treatment effect because the incidence gap between current and former smokers was fairly large and consistent with age. As a result, moving individuals from current to former smoker yielded a greater reduction in COPD cases than in outcomes with smaller current versus former smoker differences.

Table E3.1. Lifetime Clinical Outcomes for the Base Case

Treatment	Smoke-Free Years	Cardiovascular Disease Events	COPD Cases	Lung Cancer Cases
Cytisinicline + Behavioral Support	6.02	155*	168*	23*
Varenicline + Behavior Support	5.93	155*	168*	23*
Behavioral Support Alone	5.42	155*	172*	23*

evLYs: equal value of life years gained, QALY: quality-adjusted life year

*Per 1,000 individuals

E4. Sensitivity Analyses

We conducted one-way sensitivity analyses to identify the impact of parameter uncertainty and key drivers of model outcomes. The tornado diagrams (Figures E4.1 and E4.2) and ranges of inputs and resultant cost-effectiveness ratios (Tables E4.1 and E4.2) from the health care sector showed the most influential inputs generally involved the treatment effects of the smoking cessation interventions and costs of cytisinicline. Probabilistic sensitivity analyses were also performed by jointly varying all model parameters over 1,000 simulations, then calculating 95% credible range estimates for each model outcome based on the results. We also performed threshold analyses for drug costs across a range of incremental cost-effectiveness ratios ($50,000, $100,000, $150,000, and $200,000 per QALY and evLY gained). The results are shown in Tables E4.3 through E4.6.

Figure E4.1. Tornado Diagram for Cytisinicline and Behavior Support Versus Varenicline and Behavioral Support

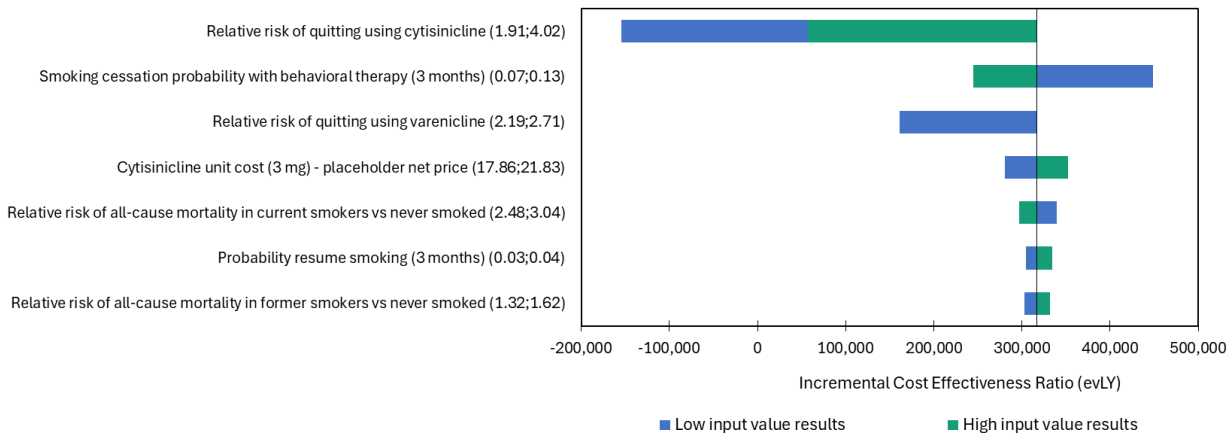


Figure E4.2. Tornado Diagram for Cytisinicline and Behavior Support Versus Behavioral Support Alone

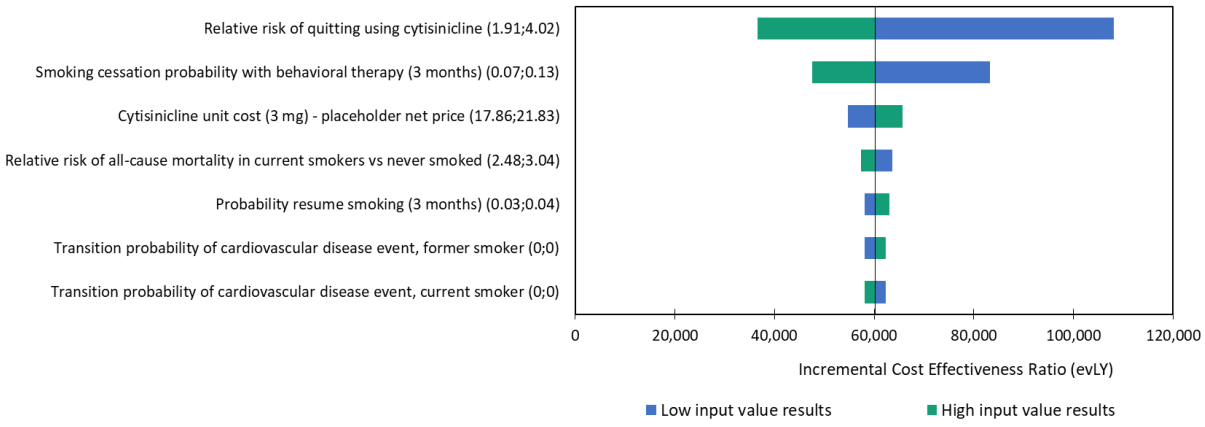


Table E4.1. Tornado Diagram Inputs and Results for Cytisinicline and Behavioral Support Versus Varenicline and Behavioral Support

	Lower Incremental CE Ratio	Upper Incremental CE Ratio	Lower Input*	Upper Input*
Relative Risk of Quitting Using Cytisinicline and Behavioral Support vs. Behavior Support Alone	-154,000	57,200	1.91	4.02
Smoking Cessation Probability with Behavioral Support Alone	245,000	448,000	0.07	0.13
Relative Risk of Quitting Using Varenicline and Behavioral Support vs. Behavior Support Alone	161,000	Undefined†	2.19	2.71
Cytisinicline Unit Cost	281,000	353,000	17.86	21.83
Relative Risk of All-Cause Mortality in Current Smokers vs. Never Smokers	297,000	340,000	2.48	3.04
Probability Resume Smoking (3 Months Cycle)	304,000	334,000	3.07%	3.74%
Relative Risk of All-Cause Mortality in Former Smokers vs. Never Smokers	303,000	332,000	1.32	1.62

CE: cost-effectiveness

*Note lower input may reflect either upper or lower ICER value depending on the direction that the input has on the ICER output.

†With equal effectiveness (RR=2.71) for both varenicline and cytisinicline, the incremental life-years, QALYs, and evLYs is 0 and the incremental cost-effectiveness ratio is undefined

Table E4.2. Tornado Diagram Inputs and Results for Cytisinicline and Behavior Support Versus Behavioral Support Alone

	Lower Incremental CE Ratio	Upper Incremental CE Ratio	Lower Input*	Upper Input*
Relative Risk of Quitting Using Cytisinicline and Behavioral Support vs. Behavior Support Alone	36,600	108,000	1.91	4.02
Smoking Cessation Probability with Behavioral Support Alone	47,600	83,300	0.07	0.13
Cytisinicline Unit Cost	54,700	65,700	17.86	21.83
Relative Risk of All-Cause Mortality in Current Smokers vs. Never Smokers	57,300	63,600	2.48	3.04
Probability Resume Smoking (3 Months Cycle)	58,200	63,000	3.07%	3.74%
Transition Probability of Cardiovascular Disease Event, Former Smoker	58,100	62,400	0.26%	0.32%
Transition Probability of Cardiovascular Disease Event, Current Smoker	58,100	62,400	0.28%	0.34%

CE: cost-effectiveness

*Note lower input may reflect either upper or lower ICER value depending on the direction that the input has on the ICER output.

Table E4.3. Results of Probabilistic Sensitivity Analysis for Cytisinicline and Behavior Support Versus Varenicline and Behavioral Support

	Cytisinicline and Behavioral Support Mean	Varenicline and Behavioral Support Mean	Incremental
Costs	$195,000	$190,000	$4,400
QALYs	10.72	10.70	0.01
evLYs	10.72	10.70	0.02

CE: cost-effectiveness, evLYs: equal-value life year, QALY: quality-adjusted life year

Table E4.4. Results of Probabilistic Sensitivity Analysis for Cytisinicline and Behavior Support Versus Behavioral Support Alone

	Cytisinicline and Behavioral Support Mean	Behavioral Support Alone Mean	Incremental
Costs	$195,000	$189,000	$5,500
QALYs	10.72	10.63	0.09
evLYs	10.72	10.63	0.09

CE: cost-effectiveness, evLYs: equal-value life year, QALY: quality-adjusted life year

Table E4.5. Probabilistic Sensitivity Analysis Cost per QALY Gained Results

	Cost Effective at $50,000 per QALY Gained*	Cost Effective at $100,000 per QALY Gained*	Cost Effective at $150,000 per QALY Gained*	Cost Effective at $200,000 per QALY Gained*
Cytisinicline + Behavioral Support vs. Varenicline + Behavioral Support	0.40%	12.00%	25.10%	34.50%
Cytisinicline + Behavioral Support vs. Behavioral Support Alone	17.10%	89.30%	98.60%	99.90%

QALY: quality-adjusted life year

*Based on placeholder price

Table E4.6. Probabilistic Sensitivity Analysis Cost Per evLY Gained Results

	Cost Effective at $50,000 per evLY Gained*	Cost Effective at $100,000 per evLY Gained*	Cost Effective at $150,000 per evLY Gained*	Cost Effective at $200,000 per evLY Gained*
Cytisinicline + Behavioral Support vs. Varenicline + Behavioral Support	1.60%	17.70%	33.20%	44.60%
Cytisinicline + Behavioral Support vs. Behavioral Support Alone	24.10%	92.30%	99.50%	99.90%

evLYs: equal value of life years gained

* Based on placeholder price

E5. Scenario Analyses

We conducted scenario analyses that include:

1. Modified societal perspective that includes components such as caregiver disutilities and costs of cigarettes avoided.
2. Undiscounted costs and outcomes
3. Using the lowest generic price for varenicline from Redbook.
4. A lower relapse probability of 1.00% starting year 5 of the model
5. Exclusion of unrelated (non-drug) health care costs that are not related to the intervention or the condition *per se*.

Table E5.1. Scenario Analysis Results (Total Outcomes)

Scenario 1: Modified Societal Perspective					
Treatment	**Drug Cost***	**Total Cost***	**QALYs**	**evLYs**	**LYs**
Cytisinicline + Behavioral Support	$5,200	$215,000	10.49	10.49	13.97
Varenicline + Behavioral Support	$880	$211,000	10.47	10.47	13.96
Behavioral Support Alone	$220	$211,000	10.40	10.40	13.89
Scenario 2: Undiscounted Costs and Outcomes					
Treatment	**Drug Cost***	**Total Cost***	**QALYs**	**evLYs**	**LYs**
Cytisinicline + Behavioral Support	$5,200	$272,000	14.37	14.38	18.68
Varenicline + Behavioral Support	$890	$267,000	14.36	14.36	18.66
Behavioral Support Alone	$220	$266,000	14.26	14.26	18.55
Scenario 3: Minimum Price for Varenicline					
Treatment	**Drug Cost***	**Total Cost***	**QALYs**	**evLYs**	**LYs**
Cytisinicline + Behavioral Support	$5,200	$195,000	10.72	10.72	13.97
Varenicline + Behavioral Support	$250	$190,000	10.71	10.71	13.96
Scenario 4: Lower Relapse Probability Starting in Year 5					
Treatment	**Drug Cost***	**Total Cost***	**QALYs**	**evLYs**	**LYs**
Cytisinicline + Behavioral Support	$5,200	$201,000	11.00	11.01	14.26
Varenicline + Behavioral Support	$880	$196,000	10.99	10.99	14.24
Behavioral Support Alone	$220	$195,000	10.91	10.91	14.16
Scenario 5: Removing Unrelated Costs					
Treatment	**Drug Cost***	**Total Cost***	**QALYs**	**evLYs**	**LYs**
Cytisinicline + Behavioral Support	$5,200	$39,200	10.72	10.72	13.97
Varenicline + Behavioral Support	$880	$34,900	10.71	10.71	13.96
Behavioral Support Alone	$220	$34,400	10.63	10.63	13.89

*Placeholder price

Table E5.2. Scenario Analysis Results (Total Outcomes)

Scenario 1: Modified Societal Perspective	**Treatment**	**Comparator**	**Cost per QALY Gained**	**Cost per evLY Gained**	**Cost per Life Year Gained**
	Cytisinicline + Behavioral Support	Varenicline + Behavioral Support	$321,000	$294,000	$335,000
	Cytisinicline + Behavioral Support	Behavioral Support Alone	$48,000	$44,000	$50,100
Scenario 2: Undiscounted Costs and Outcomes	**Treatment**	**Comparator**	**Cost per QALY Gained**	**Cost per evLY Gained**	**Cost per Life Year Gained**
	Cytisinicline + Behavioral Support	Varenicline + Behavioral Support	$249,000	$232,000	$242,000
	Cytisinicline + Behavioral Support	Behavioral Support Alone	$50,600	$47,000	$49,200
Scenario 3: Minimum Price for Varenicline	**Treatment**	**Comparator**	**Cost per QALY Gained**	**Cost per evLY Gained**	**Cost per Life Year Gained**
	Cytisinicline + Behavioral Support	Varenicline + Behavioral Support	$388,000	$403,000	$363,000
Scenario 4: Lower Relapse Probability Starting in Year 5	**Treatment**	**Comparator**	**Cost per QALY Gained**	**Cost per evLY Gained**	**Cost per Life Year Gained**
	Cytisinicline + Behavioral Support	Varenicline + Behavioral Support	$292,000	$274,000	$302,000
	Cytisinicline + Behavioral Support	Behavioral Support Alone	$57,300	$53,800	$59,200
Scenario 5: Removing Unrelated Costs	**Treatment**	**Comparator**	**Cost per QALY Gained**	**Cost per evLY Gained**	**Cost per Life Year Gained**
	Cytisinicline + Behavioral Support	Varenicline + Behavioral Support	$331,000	$309,000	$343,000
	Cytisinicline + Behavioral Support	Behavioral Support Alone	$56,000	$52,400	$58,100

E6. Model Validation

Model validation followed standard practices in the field. We tested all mathematical functions in the model to ensure they were consistent with the report (and supplemental Appendix materials). We also conducted sensitivity analyses with null input values to ensure the model was producing findings consistent with expectations. Further, independent modelers tested the mathematical functions in the model as well as the specific inputs and corresponding outputs.

Model validation was also conducted in terms of comparisons to other model findings. We searched the literature to identify models that were similar to our analysis, with comparable populations, settings, perspective, and treatments.

Prior Economic Models

In our assessment of cytisinicline versus behavioral therapy alone, we found similar results for incremental QALYs to prior assessments that looked at varenicline versus behavioral therapy alone. We did not identify any assessments of cytisinicline versus behavioral therapy alone for our intended population, but because in our clinical effectiveness estimates, cytisinicline and varenicline had similar treatment effects, a cost-effectiveness analysis of varenicline versus behavioral therapy alone comparison would provide a face validity check. In the prior CEAs that we found for varenicline versus behavioral therapy alone (or unassisted quit attempts), we found that the incremental QALY gains were 0.05, 0.08, 0.08, 0.11, 0.14 and 1.09 with the last estimate being the outlier.[27,92-96] Our estimate of 0.08 for cytisinicline versus behavioral therapy alone is therefore similar to the results found in most other models. This is especially true for the two models that also used the BENESCO framework and from the US setting, both of which found QALY gains of 0.08.[27,94]

We found two prior CEAs that compared cytisinicline versus varenicline. In one study based in the UK that used the BENESCO framework, the LY and QALY gains were 0.03 and 0.03, respectively. The treatment effect estimates used in this study were informed by an NMA that the authors conducted, and they concluded that the clinical effectiveness in terms of quit rate probability between the two treatments was not significant as the 95% CrI included 0 (-0.048, 0.389).[34] This was consistent with ICER's internal NMA. The other model was a slightly different comparison as the authors assessed the effect of adding cytisinicline to the UK's smoking cessation program and assumed 50% of varenicline users would receive cytisinicline instead.[97] This amounted to only 5% of eligible smokers. They estimated that cytisinicline would generate 0.0014 QALY gains but this is not a directly comparable estimate to our pairwise incremental QALYs. Even so, the finding of small incremental QALY gains between the two drugs is consistent with our model of 0.01 gains in LYs and QALYs. In most of our comparisons to prior models, cross-country variation in downstream medical costs further limited direct comparison of total costs and resultant incremental cost-effectiveness ratios across studies.

F. Potential Budget Impact: Supplemental Information

Methods

We used results from the same model employed for the cost-effectiveness analyses to estimate total potential budget impact. Potential budget impact was defined as the total differential cost of using each new therapy rather than relevant existing therapy for the treated population, calculated as differential health care costs (including drug costs) minus any offsets in these costs from averted health care events. All costs were undiscounted and estimated over one- and five-year time horizons.

This budget impact analysis included the estimated number of individuals in the US who would be eligible for cytisinicline. To estimate the size of the potential candidate population, we used inputs for the percentage of adults who smoke cigarettes (11.6%) and the percentage of adults who are interested in quitting (67.7%).[6] Applying these sources to the total US population of adults averaged over the next five years (270,906,499) results in estimates of 21,274,829 eligible patients in the US. For the purposes of this analysis, we assume that 20% of these patients would initiate treatment in each of the five years, or 4,254,965 patients per year.[56] At baseline, we assumed that 10% of the eligible population is being treated with varenicline with behavioral support, and 90% are being treated with behavioral support alone.[57]

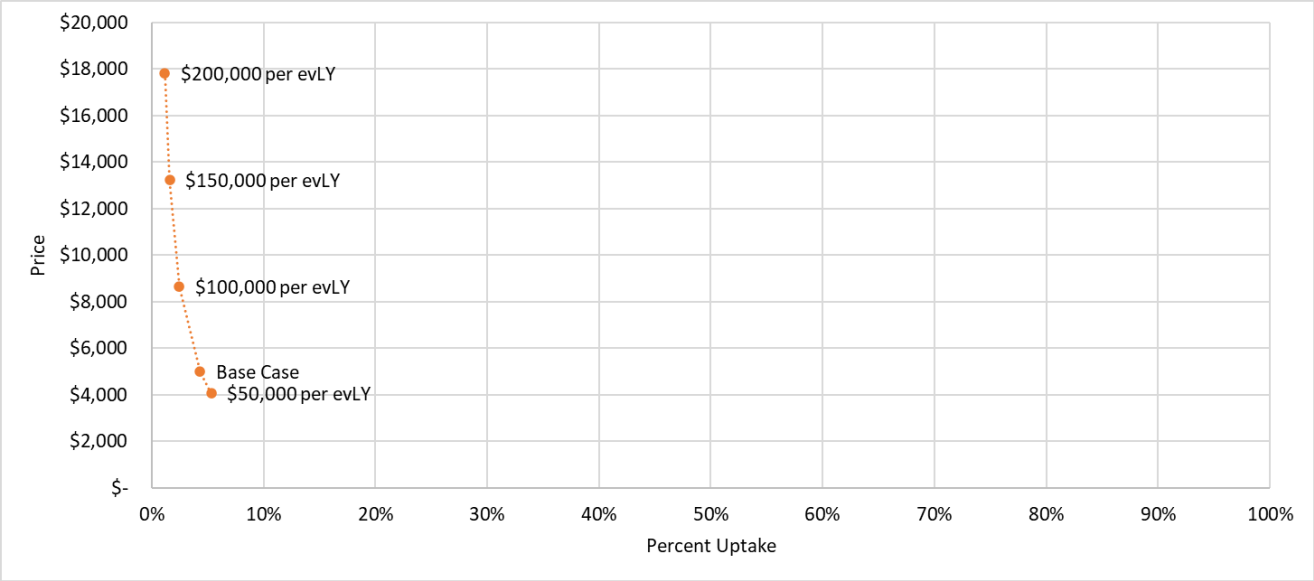
ICER's methods for estimating potential budget impact are described in detail elsewhere and have recently been updated.[98,99] The intent of our revised approach to budgetary impact is to document the percentage of patients that could be treated at selected prices without crossing a budget impact threshold that is aligned with overall growth in the US economy.

Once estimates of budget impact are calculated, we compare our estimates to an updated budget impact threshold that represents a potential trigger for policy mechanisms to improve affordability, such as changes to pricing, payment, or patient eligibility. As described in ICER's methods presentation (Value Assessment Framework), this threshold is based on an underlying assumption that health care costs should not grow much faster than growth in the overall national economy. From this foundational assumption, our potential budget impact threshold is derived using an estimate of growth in US gross domestic product (GDP) +1%, the average number of new drug approvals by the FDA over the most recent two-year period, and the contribution of spending on retail and facility-based drugs to total health care spending.

For 2024-2025, therefore, the five-year annualized potential budget impact threshold that should trigger policy actions to manage access and affordability is calculated to total approximately $880 million per year for new drugs.

Figure 7.2 in the main report shows the percentage of eligible patients that could be treated with cytisinicline at the threshold prices when compared to varenicline with behavioral support before reaching the budget impact threshold. Figure F1.1 below shows the percentage of eligible patients that could be treated with cytisinicline at the threshold prices when compared to behavioral support alone. At the $50,000, $100,000, $150,000 and $200,000 per evLY threshold prices for cytisinicline compared to behavioral support alone, ($4,000, $8,600, $13,000, and $17,800), 5.3%, 2.5%, 1.6%, and 1.2% of patients could be treated before reaching the potential budget impact threshold (Figure F1.1).

Figure F1. Percentage of Eligible Patients Treated Without Reaching the Potential Budget Impact Threshold at Placeholder and Threshold Prices for Cytisinicline with Behavioral Support Compared to Behavioral Support Alone



evLY: equal value of life years

G. Supplemental Policy Recommendations

Payers

Drug-Specific Coverage Criteria: Cytisinicline

As noted above, cytisinicline should be treated like varenicline.

Step Therapy

If cytisinicline's price does not align with its value, then step therapy with either varenicline and/or combined nicotine replacement would be reasonable. If it is fairly-priced, then immediate availability of the first FDA-approved drug in 20 years may encourage people who smoke to make another quit attempt, which would help to reduce the burden and cost of smoking-related illness in the United States.

Clinical Coverage Criteria

- **Age:** 18 years and older.
- **Clinical eligibility**: Patients who smoke cigarettes and are interested in quitting.
- **Exclusion criteria**: End-stage renal disease, pregnancy, breastfeeding. Cytisinicline is not contraindicated in patients with serious mental illness; this should not be an exclusion criterion.
- **Dose:** 3 mg by mouth three times daily for 12 weeks.
- **Provider restrictions**: There is no need for provider restrictions.

H. Public Comments

This section includes summaries of the public comments prepared for the Cytisinicline for Smoking Cessation Public Meeting on Thursday, January 15th. These summaries were prepared by those who delivered the public comments at the meeting and are presented in order of delivery.

A video recording of all comments can be found here.

Judy Nagy
Patient Advocate

I have been a Patient Advocate for the past 17 years with The Global Healthy Living Foundation and I am a smoker. I am 71 years old and have been smoking since the age of 16. I grew up in a smoking home which was very common in the 1950's. Both of my parents were smokers. My father, who passed away in 1997 from non-Hodgkin's lymphoma, quit at the age of 60. My mother, who started smoking in her teen years, did not quit until she was diagnosed with Stage 4 lung cancer in 2008. She opted out of treatment and passed away eight months later in 2009. I want to quit smoking and I need to quit smoking. I have tried and failed many times.

I was diagnosed with Rheumatoid Arthritis at the age of 25, which prompted me to become a Patient Advocate. Over the years, I have developed many comorbidities, some of which may be attributed to smoking. It started with high blood pressure about 15 years ago. Roughly ten years ago, I was diagnosed with asthma which has since advanced to COPD.

In December of 2024, I had a chunk of my lung removed that contained a nodule that resulted in Stage 1 Adenocarcinoma. No other tissue or lymph nodes were involved and I was cancer free. A month later, I saw an ENT hoping for a permanent repair of my paralyzed vocal cord that resulted from a thyroid surgery many years ago. Instead, I was diagnosed with squamous cell carcinoma of the vocal cords. I had three laser surgeries in 2025 on my vocal cords, the most recent being December 19 which is why my voice is not very strong throughout this meeting. Because I have not quit smoking, I am still dealing with regrowth of the squamous cells in both vocal cords.

My surgeon has sent me to a psychiatrist and to a whole health counselor. I will have my first acupuncture treatment in March. The counselor went over quite a few suggestions that were very helpful. However, there are stressors and triggers that continue to draw to continue smoking. One would think that being a retired senior would be stress free, but life has its challenges at all ages. We still deal with the stressors of everyday life.

I do believe that, in addition to counseling, peer to peer / patient to patient counseling is important.

There is stigma that presses on those that smoke in what is now basically a smokeless society. The stigma comes from the pressure of others on smokers in our inability to quit. In my attempts to quit, I found that patches, lozenges, and certain medications did nothing to help. I did, however, have a three-month period of quitting when I moved to another state. The new surroundings and atmosphere were helpful until the triggers and stressors brought me back to smoking.

In the discussion of vaping as a viable option, I believe it has no real benefit to quitting as it still provides the nicotine driver. I know many that believe they have quit because they resorted to vaping, but there are still long-term effects, and many have become as dependent on vaping as they were smoking cigarettes.

I am encouraged that there is a medication that is being reviewed by the FDA for distribution in the United States. In listening to the doctors, pharmacists, clinicians, and advocates in this meeting, and hearing the evidence of cytisinicline being prescribed in Europe for the past 50 years, my response is *"I trust the data and I don't care where it comes from!"*

It has been many years since a new medication has come on the market, and I believe anything new would be an opportunity to entice smokers to try to quit once again. While it might not work for all, it provides a path to a new chance for success. I hope that it will be available without the need for trial and error of any other medication, be affordable, and a comprehensive option for those who have tried unsuccessfully in the past. Additional support through behavioral therapy, educational material, and peer support is important as well.

I sincerely appreciate the opportunity to share my story, thoughts and views in this important meeting as a patient and patient advocate. I sincerely hope that I will be able to try this new medication should it become available to the public in the United States.

Judy Nagy

I. Conflict of Interest Disclosures

Tables I1 through I3 contain conflict of interest (COI) disclosures for all participants at the Thursday, January 15th public meeting of cytisinicline for Smoking Cessation. You can find any conflicts reported by the authors of the report, or expert reviewers, on page v.

Table I1. Midwest CEPAC Panel Member Participants and Conflict of Interest Disclosures

Midwest CEPAC Member	Conflict of Interest
Eric Armbrecht, PhD Professor and Associate Provost, Saint Louis University Center for Health Outcomes Research, School of Medicine and College for Public Health & Social Justice	No conflicts to disclose.
Alan Balch, PhD Chief Executive Officer, Patient Advocate Foundation and the National Patient Advocate Foundation	No conflicts to disclose.
Bijan Borah, PhD Professor of Health Services Research, Mayo Clinic College of Medicine and Science Consultant, Division of Health Care Policy and Research, Department of Health Sciences Research, Mayo Clinic Joint Appointment as a Consultant, Department of Obstetrics and Gynecology, Mayo Clinic	No conflicts to disclose.
Kurt Vanden Bosch, PharmD System Formulary Manager, St. Luke's Health System, Idaho	No conflicts to disclose.
Donald Casey, MD, MPH, MBA, MACP, FAHA, DFACMQ, DFAAPL, CPE Associate Professor of Internal Medicine, Rush Medical College Adjunct Professor of Healthcare Quality & Safety and Population Health, Thomas Jefferson University College of Population Health Affiliate Faculty, Institute for Healthcare Informatics, University of Minnesota Faculty, Artificial Intelligence in Cardiology Program (ATRIA)	No conflicts to disclose.
Yngve Falck-Ytter, MD, AGAF Professor of Medicine, Case Western Reserve University; Chief, Gastroenterology and Hepatology VA Northeast Ohio Healthcare System, Cleveland	No conflicts to disclose.
Heather Guidone, BCPA Program Director, Center for Endometriosis Care (CEC)	No conflicts to disclose.
Jayani Jayawardhana, PhD Associate Professor, Health Management & Policy, University of Kentucky's College of Public Health	No conflicts to disclose.

Midwest CEPAC Member	Conflict of Interest
Jill Johnson, PharmD Professor, Department of Pharmacy Practice, University of Arkansas for Medical Sciences College of Pharmacy	As part of her income at the UAMS College of Pharmacy, she has support from one of their service divisions, the Evidence-based Prescription Drug Program. Through this, she has intellectual property income through UAMS Bioventures that exceeds $1000/year.
David Kim, PhD Assistant Professor of Medicine at the University of Chicago	No conflicts to disclose.
Timothy McBride, PhD Bernard Becker Professor, School of Public Health, Washington University in St. Louis Co-Director, Center for Advancing Health Services, Policy & Economics Research (CAHSPER) Co-Director, Policy and Structural Solutions (PS2) Innovation Research Network	No conflicts to disclose.
Reem Mustafa, MD, MPH, PhD Professor of Medicine, Division of Nephrology and Hypertension Director, Outcomes and Implementation Research, University of Kansas Medical Center	No conflicts to disclose.
Rachel Sachs, JD, MPH Professor of Law, Washington University in St. Louis Faculty Scholar, Washington University in St. Louis Institute for Public Health	No conflicts to disclose.
Timothy Wilt, MD, MPH Professor of Medicine, Core Investigator, and Staff Physician at the Minneapolis VA Center for Chronic Disease Outcomes Research, University of Minnesota School of Medicine	No conflicts to disclose.

Table I2. Clinical and Patient Experts and Conflict of Interest Disclosures

Clinical and Patient Experts	Conflict of Interest
Mike Hess Senior Director of Advocacy & Regulatory Affairs, COPD Foundation	80% of COPD Foundation's annual funding is from health care companies.
Hayden McRobbie, MB ChB, PhD Professor of Population Health, Queen Mary University of London	No conflicts to disclose.
Judy Nagy Patient Advocate	Judy Nagy volunteers with AiArthritis, Arthritis Foundation, and the Global Healthy Living Foundation and does not receive income from these organizations.
Nancy Rigotti, MD Professor of Medicine, Harvard Medical School; Director, Tobacco Research & Treatment Center, Massachusetts General Hospital	Dr. Nancy Rigotti has received research funding through Massachusetts General Hospital from Achieve Life Sciences, Inc. for conducting clinical trials of cytisinicline. She received consulting fees from Achieve Life Sciences through the end of 2022, but not since that time.

Table I3. Health Care Companies and Conflict of Interest Disclosures

Health Care Company Representatives	Conflict of Interest
Benjamin Broder, MD, PhD Regional Assistant Medical Director of Quality and Clinical Analysis, Kaiser Permanente	Dr. Benjamin Broder is a full time employee of Kaiser Permanente.
Peter A. Glassman, MBBS, MSc, FACP Chair, Medical Advisory Panel, Veterans Affairs Pharmacy Benefits Management Services	Dr. Peter Glassman is a full time employee of the Department of Veterans Affairs.
Julia Logan, MD, MPH Chief Clinical Director, CalPERS	Dr. Julia Logan is a full time employee of CalPERS.