ACHIEVE
LIFE SCIENCES

June 10, 2025

Sarah K. Emond, MPP
President and Chief Executive Officer
Institute for Clinical and Economic Review
14 Beacon Street, Suite 800
Boston, MA 02108

Subject: Draft Scoping Document for Review of Cytisinicline for Smoking Cessation

Dear Ms. Emond:

Achieve Life Sciences appreciates the opportunity to comment on the draft scoping document outlining ICER's approach to reviewing cytisinicline for smoking cessation. Smoking represents a serious, life-threatening public health crisis that continues to impose a significant burden on morbidity and mortality in the United States and costs over $300 billion annually in healthcare spending and productivity losses. Cytisinicline has demonstrated the potential for significant improvement over existing therapies in both efficacy and tolerability. As you point out, FDA approval of a new treatment option for smoking cessation has not occurred for nearly two decades and there is a continued unmet public health need. Effective use of cytisinicline could lead to measurable population health benefits, including thousands of additional successful quitters with life-years gained.

GENERAL COMMENTS

On page 2 of the Draft Background and Scope, the document reads, "[T]he focus of this review is a potential new therapy, cytisinicline, also known as cytisine." To clarify, cytisinicline and the older ex-U.S. cytisine products are very different and distinct treatments. The FDA considers cytisinicline as a "new molecular entity" (NME). A NME is an active ingredient that contains no active moiety that has been previously approved by the Agency in an application submitted under section 505 of the Federal Food, Drug, and Cosmetic Act, or has been previously marketed as a drug in the U.S. Achieve Life Sciences (Achieve) filed an Investigational New Drug (IND) application in 2017 for developing cytisinicline as a new treatment for nicotine dependence and will soon be filing a New Drug Application (NDA) with the FDA. Ex-U.S., cytisine is given in a complex 25-day treatment regimen with the dosage starting at six 1.5 mg tablets daily for the first three days, then with a specific reduction schedule over three weeks ending with one 1.5mg dosage on the last day. In trials, Achieve has optimized cytisinicline treatment using a novel tablet dosing, revised schedule, and longer treatment durations: a 3 mg tablet formulation given orally three times per day (TID) for 6 or 12or12 weeks. The formulation, dosage and duration of treatment are unique to cytisinicline. Cytisinicline used in the Achieve Life Sciences product is being manufactured under strict GMP standards required for distribution and use in the U.S. with additional purification not present in the manufacture of cytisine. In short, the Achieve-developed cytisinicline product is distinct from the older ex-U.S. cytisine product.

Achieve Life Sciences has conducted extensive research for this new cytisinicline product, including all non-clinical data requirements by FDA for an NME as well as completing all required Phase 1, Phase 2 and Phase 3 clinical studies. Phase 1 studies have established the maximum tolerated dose, food-effects based on the new formulation, cardiac TQT effects of the new treatment regimen as well as renal impairment influences on dosing. Phase 3 results have demonstrated the new efficacy, tolerability and safety of this 3 mg pill formulation, TID regimen, and 6 week vs 12 week cytisinicline treatment durations for smoking cessation.

In two large Phase 3 trials (ORCA-2 and ORCA-3), cytisinicline treatment regimens for 6 or 12 weeks were significantly more effective than placebo treatment with standard behavioral support (as the control) in achieving long-term (through Week 24) smoking cessation success as demonstrated by odds ratios (ORs) below.

- ORCA-2: At Week 24, continuous abstinence rates remained significantly higher than placebo plus behavioral support for:
  - 6-weeks: abstinence from Week 3 to 24: OR 3.7 (95%CI, 1.5–10.2; P = .002);
  - 12-weeks: abstinence from Week 9 to 24: OR 5.3 (95%CI, 2.8–11.1; P < .001)
- ORCA-3: Replicated these findings with:
  - 6-weeks: abstinence from Week 3 to 24: OR 6.3 (95%CI, 1.9–34.6; P < .001);
  - 12-weeks: abstinence from Week 9 to 24: OR 5.8 (95%CI, 2.9–12.4; P < .001)

While no direct head-to-head trial comparisons have been conducted, the efficacy for cytisinicline in ORCA-2 and ORCA-3 (as demonstrated by ORs) was higher than what has been reported for other prescription therapies (Anthenelli, 2016) including varenicline (OR of 2.7 for Week 9 to 24 continuous abstinence) and bupropion (OR of 1.8 for Week 9 to 24 continuous abstinence). In addition, smokers who had previously unsuccessfully used both varenicline and bupropion to quit smoking, achieved long-term smoking cessation through Week 24 when treated with cytisinicline for 6 or 12 weeks, compared to placebo with standard behavioral support.

REPORT AIM

Cytisinicline is successful in supporting those who want to quit smoking because it treats the underlying nicotine dependence that comes from smoking cigarettes. We respectfully suggest, as outlined below, that ICER consider not only the efficacy of various products for smoking cessation, but also their success in treating the nicotine dependence that results from smoking.

COMMENTS ON PICOTS

Populations: According to the U.S. Centers for Disease Control and Prevention (CDC), in 2022, 67.7% of adults who smoked said they wanted to quit smoking and 53.3% of adults who smoked said they had tried to quit in the past year. However, only 8.8% of adults who smoked were able to successfully quit smoking in 2022. As ICER reviews the relative efficacy of various smoking cessation treatments, approaches and therapies, it is important to note that patients in cytisinicline Phase 3 trials had a mean of 6.5 prior quit attempts using currently available methods; yet this population was significantly more

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likely to successfully quit using cytisinicline. Such prior, unsuccessful quit attempts are relevant when reviewing the data.

Comparators: Achieve Life Sciences respectfully suggests that ICER consider only those comparators that have been approved by the FDA for smoking cessation. The FDA has not approved any electronic cigarettes containing nicotine for smoking cessation. There are multiple nicotine-containing products promoted, but not approved, as tools to assist smokers in quitting cigarettes, such as electronic cigarettes, nicotine pouches (Zyn, etc.). All contain nicotine and thus, do not treat the underlying nicotine dependence problem. Most importantly, none have been approved by the FDA as a smoking cessation product. We respectfully suggest that ICER consider only those products approved for smoking cessation as comparators for cytisinicline.

Outcomes: In addition to measuring "abstinence from cigarette smoking or a decrease in cigarettes smoked per day," Achieve believes it is imperative to consider the impact of ongoing nicotine dependence that results from the use of comparator nicotine containing devices. The majority of tobacco users find themselves dependent on nicotine to some extent, especially those who want to quit but are unable to quit. Nicotine releases dopamine in the same regions of the brain as other addictive drugs. It causes mood-altering changes that make the person temporarily feel good. Nicotine is extremely addictive, comparable to opioids, alcohol and cocaine. Nicotine poses multiple health hazards. Nicotine exposure may pose an increased risk of exacerbating cardiovascular disease. Nicotine also poses ill impacts on reproductive health. As ICER reviews cytisinicline comparators and outcomes, it is essential that the costs of managing and treating ongoing nicotine dependence resulting from the use of comparators that contain nicotine are considered alongside abstinence from nicotine by achieving smoking cessation.

SCOPE OF COMPARATIVE VALUE ANALYSIS

In considering the health outcomes of interventions, we encourage ICER to take an inclusive view of "smoking-attributable conditions avoided." In addition to COPD, coronary heart disease, stroke and lung cancer (as outlined in the Draft Scoping document), smoking is known to increase the risk of macular degeneration, type 2 diabetes, ectopic pregnancy, a loss of bone density with an increased risk of fractures, colorectal cancer and rheumatoid arthritis, among other impacts. Further, research shows that quitting smoking lowers the risk of multiple cancers including cancers of the lung, larynx, oral cavity and pharynx, esophagus, pancreas, bladder, stomach, colon and rectum, liver, cervix, kidney, and acute myeloid leukemia (AML).

Thank you for the opportunity to submit our comments. For additional information, or if you have any questions, please contact Dr. Mark Rubinstein at mrubinstein@achievelifesciences.com. We look forward to working with ICER as its review of cytisinicline progresses.

Sincerely,

Mark Rubinstein, M.D.
VP, Head of Medical Affairs

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20 May 2025

Greetings,

I am writing to briefly offer commentary on ICER's forthcoming review on treatments for smoking cessation. I understand that this assessment will compare a novel product, cystinicline, to a variety of comparators, including behavioral therapy, nicotine replacement products (including patches combined with short-acting agents), electronic nicotine delivery systems, varenicline (alone or in combination with nicotine replacement products), and bupropion. The outcomes of interest will include abstinence from cigarette smoking or a decrease in cigarettes smoked per day. I would like to offer an additional comparator and an additional outcome for consideration.

First, the US Food and Drug Administration recently approved the marketing of nicotine transmucosal pouches. Much like electronic nicotine delivery systems, these products may provide a harm reduction approach to smoking; however, I strongly suspect that long-term studies will need to be conducted on both these products and electronic nicotine delivery systems before definitive statements about health benefits can be made. Regardless, these products are on the market in the United States, and likely deserve similar consideration to electronic nicotine delivery systems.

Second, I feel it may be appropriate to discuss so-called "smokeless" tobacco products. These products—which include chewing tobacco, snuff, and snus—are not without harms, including increased rates of cancer and cardiovascular events. The Centers for Disease Control and Prevention state that about 2% of US adults used smokeless tobacco products in 2021. Information about the harms associated with smokeless tobacco, and how it can be discontinued, may be relevant to the analysis. I can imagine a Markov chain-style model that incorporates use of smokeless tobacco products as an alternative to smoking; however, I have serious doubts that there is enough information in the literature to population such a model. Regardless, smokeless tobacco may merit a narrative mention, if nothing else.

I hope these comments are helpful. If I may clarify, please feel free to reach out to me via email at roncarjr@gmail.com.

Sincerely,

Ronald L Carico Jr, PharmD-MPH
Psychiatric Clinical Pharmacist
Marshall Health
Huntington WV

Comments on ICER document:

Cytisinicline for Smoking Cessation Draft Background and Scope (May 20, 2025, version)

Nancy A. Rigotti, MD & Krishna P. Reddy, MD, MS

Tobacco Research & Treatment Center, Massachusetts General Hospital, Harvard Medical School

Thank you for the opportunity to review and comment on this document. I have shared this document with my colleague, Krishna Reddy, MD, MS, Associate Professor of Medicine, Harvard Medical School, and investigator in the Mass General Hospital Tobacco Research and Treatment Center. Both of us have reviewed the document and we submit these comments jointly.

First, we believe that the draft scope is very strong and the analysis planned is thoughtful.

Second, regarding the plan to develop a cost-effectiveness model, we have these questions:

- How will you account for differential mortality risks by smoking status?
- How will you account for differential health care costs by smoking status?
- Why use a one-year cycle state for smoking status? Changes in behaviors occur at a shorter time horizon, and many tobacco cessation trials do not follow participants for one year.
- For model inputs, "clinical probabilities" are mentioned. Specifically, what will these be?

Third, given the plan to develop an economic model for the proposed analysis of cytisine, we would like to make the team aware of the existing Simulation of Tobacco and Nicotine Outcomes and Policy (STOP) model,[1-3] a microsimulation model developed by Dr. Reddy that might be a useful tool or model for the work planned.

References

[1] Reddy KP, Bulteel AJB, Levy DE, Torola P, Hyle EP, Hou T, Osher B, Yu L, Shebl FM, Paltiel AD, Freedberg KA, Weinstein MC, Rigotti NA, Walensky RP. Novel microsimulation model of tobacco use behaviours and outcomes: calibration and validation in a US population. *BMJ Open* 2020;10:e032579. doi:10.1136/bmjopen-2019-032579.

[2] Schwamm E, Noubary F, Rigotti NA, Reddy KP. Longitudinal transitions in initiation, cessation, and relapse of cigarette smoking and e-cigarette use among US youth and adults: Validation of a microsimulation model. *PLoS ONE* 2023;18(4): e0284426. https://doi.org/10.1371/journal.pone.0284426

[3] Levy, D.E., Lee, S.S., Qian, Y., Shebl FM, Goldberg SL, Mulroy NM, Anderson NK, Hyle EP, Becker FE. Reddy KP. Disparities in cigarette smoking and the health of marginalized populations in the U.S.: a simulation analysis. *BMC Public Health* 2025; **25**, 1546. https://doi.org/10.1186/s12889-025-22658-8

To: **publiccomments@icer.org**

From: Mitchell Berger, (comments made in personal capacity), mazruia@hotmail.com. May 23, 2025

Re: Institute for Clinical and Economic Review to Assess Treatment for Smoking Cessation, https://myemail.constantcontact.com/Institute-for-Clinical-and-Economic-Review-to-Assess-Treatment-for-Smoking-Cessation.html (Cytisinicline for Smoking Cessation)

To whom it may concern: In response to the above Draft Background and Scope for the Cytisinicline for Smoking Cessation review, I write to make the following suggestions. Please note that while I have worked for federal and local public health agencies, the views expressed are mine alone and should not be imputed to other individuals nor to any agency or organization.

- **Define behavioral support**: With respect to interventions, the draft scoping review states that ICER will evaluate "Cytisinicline with behavioral support." However, I am unclear what is meant by 'behavioral support.' Does ICER intend to evaluate counseling? Contingency management/incentives? Quitlines? Use of text messages? Other approaches or combinations of approaches? Also, would these services be provided face-to-face; via telehealth/online; in individual settings or groups; through other means; or a combination of approaches.[1]In the final scoping review, I recommend ICER more carefully and specifically define the meaning of 'behavioral support.'
- **Note if pediatric populations will be included and define age ranges for children and adults**: The scoping review does mention that "we will explore data in the population of individuals, youth and adults, interested in quitting electronic cigarettes (vaping)." However, a table (1.1) includes data only on those 18 and above. It is not entirely clear (to me) whether ICER intends to evaluate Cytisinicline for Smoking Cessation in youth (<18) as well as adults. Given the high levels of tobacco product use among children and youth[2] and barriers to quitting,[3] I recommend including <18 populations in this evaluation if feasible. If pediatric populations are included the age group should be expressly defined (e.g., under 18, under 21, etc.).
- **Consider additional outcome measures**: The draft scoping review indicates that ICER will consider among outcomes "Abstinence from cigarette smoking or a decrease in

[1] Hartmann-Boyce J, Livingstone-Banks J, Ordóñez-Mena JM, Fanshawe TR, Lindson N, Freeman SC, Sutton AJ, Theodoulou A, Aveyard P. Behavioural interventions for smoking cessation: an overview and network meta-analysis. Cochrane Database Syst Rev. 2021 Jan 4;1(1):CD013229. doi: 10.1002/14651858; https://www.cdc.gov/tobacco-surgeon-general-reports/reports/2020-smoking-cessation/

[2] https://www.samhsa.gov/data/data-we-collect/nsduh-national-survey-drug-use-and-health/national-releases/2023; https://www.cdc.gov/tobacco/php/data-statistics/youth-data-tobacco/index.html

[3] https://www.aafp.org/pubs/afp/issues/2023/0500/letter-smoking-cessation-adolescents.html; https://smokingcessationleadership.ucsf.edu/sites/smokingcessationleadership.ucsf.edu/files/Downloads/Toolkits/AAP_Youth_Tobacco_Cessation_Considerations_for_Clinicians.pdf

cigarettes smoked per day."[4] ICER should consider more nuanced measures of abstinence (e.g., abstinence at 6 months, 1 year, etc.). Occurrence of relapses after quitting and patient satisfaction scores also could be considered.

- **Include in the Psychiatric disorders (e.g., schizophrenia and depression) subpopulation those using other licit or illicit substances**: Tobacco often is used in conjunction with other substances such as alcohol, cannabis, or opioids.[5] This may increase morbidity and mortality and make it harder to quit. Also, many of those with such conditions as schizophrenia and depression have co-occurring substance use disorders.[6] Therefore, if feasible, impacts on those (co) using other licit and illicit substances and those with co-occurring disorders may be considered.
- **Include data on pregnant and postpartum women as a subpopulation if available:** Many tobacco cessation approaches, including pharmacotherapies, may not be evaluated in pregnant and postpartum women. But to the extent data is available for Cytisinicline in this population it should be discussed.[7]

Thank you for considering this input.

Sincerely,

Mitchell Berger

[4] Cheung KL, de Ruijter D, Hiligsmann M, Elfeddali I, Hoving C, Evers SMAA, de Vries H. Exploring consensus on how to measure smoking cessation. A Delphi study. BMC Public Health. 2017 Nov 21;17(1):890. doi: 10.1186/s12889-017-4902-7.

[5] See e.g., Jude A Frie, Caitlin J Nolan, Jennifer E Murray, Jibran Y Khokhar, Addiction-Related Outcomes of Nicotine and Alcohol Co-use: New Insights Following the Rise in Vaping, *Nicotine & Tobacco Research*, Volume 24, Issue 8, August 2022, Pages 1141–1149, https://doi.org/10.1093/ntr/ntab231; Jan van Amsterdam, Wim van den Brink, The effect of alcohol use on smoking cessation: A systematic review, Alcohol, 2023; 109: 13-22 https://doi.org/10.1016/j.alcohol.2022.12.003. Chu A, Chaiton M, Kaufman P, Goodwin RD, Lin J, Hindocha C, Goodman S, Hammond D. Co-Use, Simultaneous Use, and Mixing of Cannabis and Tobacco: A Cross-National Comparison of Canada and the US by Cannabis Administration Type. Int J Environ Res Public Health. 2023 Feb 27;20(5):4206. doi: 10.3390/ijerph20054206; Lilian Custodio, Samantha Malone, Michael T. Bardo, Jill R. Turner, Nicotine and opioid co-dependence: Findings from bench research to clinical trials, Neuroscience & Biobehavioral Reviews, 2002; 134: 104507, https://doi.org/10.1016/j.neubiorev.2021.12.030; Abdolhalim Rajabi, Mohsen Dehghani, Azadeh Shojaei, Mojtaba Farjam, Seyed Abbas Motevalian, Association between tobacco smoking and opioid use: A meta-analysis, Addictive Behaviors, 2019; 92: 225-235, https://doi.org/10.1016/j.addbeh.2018.11.043.

[6] https://library.samhsa.gov/product/issue-brief-co-occurring-mental-health-and-substance-use/pep24-01-008

[7] Nikolaos Ioakeimidis, Charalambos Vlachopoulos, Vasiliki Katsi, Dimitrios Tousoulis, Smoking cessation strategies in pregnancy: Current concepts and controversies, Hellenic Journal of Cardiology, 2019; 60: 11-15, https://doi.org/10.1016/j.hjc.2018.09.001; Tobacco and Nicotine Cessation During Pregnancy, American College of Obstetricians and Gynecologists, 2023 (reaffirmed), Committee Opinion, https://www.acog.org/clinical/clinical-guidance/committee-opinion/articles/2020/05/tobacco-and-nicotine-cessation-during-pregnancy