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Achieve Life Sciences Announces Cytisinicline Phase 3 ORCA-3 Trial Publication on Smoking Cessation in JAMA Internal Medicine

ORCA-3 Demonstrated a Significant Increase in Quitting and Reduction in Nicotine Cravings for Cytisinicline-Treated Participants Compared to Placebo

Cytisinicline New Drug Application (NDA) Submission to FDA Planned for June 2025

SEATTLE and VANCOUVER, British Columbia, April 21, 2025 (GLOBE NEWSWIRE) -- Achieve Life Sciences, Inc. (Nasdaq: ACHV), a late-stage specialty pharmaceutical company focused on the global development and commercialization of cytisinicline as a treatment of nicotine dependence for smoking cessation, today announced that complete trial results from its ORCA-3 were published in the *Journal of the American Medical Association (JAMA) Internal Medicine*. ORCA-3 was the second randomized, placebo-controlled Phase 3 clinical trial evaluating cytisinicline for smoking cessation in 792 U.S. adults. The authors concluded that ORCA-3 reaffirms cytisinicline's efficacy and tolerability for smoking cessation in adult smokers at both 6- and 12-week treatment durations, including reduction in nicotine cravings and extended cessation benefits through 24 weeks.

In addition to previously reported topline results announced in May 2023, the published completed trial results provided further evidence of cytisinicline's highly targeted effect on treating nicotine dependence by binding to specific nicotine receptors. These consistent results, now published from two large, randomized Phase 3 trials, demonstrated that cytisinicline significantly reduced nicotine cravings and increased the likelihood of quitting smoking. In clinical trials, cytisinicline was well tolerated, which is thought to be due to limited other off-target binding effects that can result in side effects known to be associated with currently available treatments.

Similar to the first Phase 3 trial, ORCA-3 participants had an average age of 53 years, smoked a median of 20 cigarettes per day at baseline, and had a median smoking history of 36 years with four prior quit attempts.

“Most people who smoke want to quit and it often takes multiple attempts to do so successfully. Our trial participants were no exception and had multiple previous quit attempts, although less than half had previously tried varenicline, possibly due to its well-known adverse event profile,” said Cindy Jacobs, MD, PhD, President and Chief Medical Officer of Achieve Life Sciences. “Cytisinicline is very selective in targeting only nicotine receptors and has shown limited binding to other off-target receptors that can cause side effects, like nausea and gastrointestinal disturbances. We believe this leads to a highly tolerable treatment with cytisinicline, as demonstrated in our clinical trial program.”

Results from the ORCA-3 study show that cytisinicline significantly increased the odds of smoking cessation compared to placebo. Cytisinicline also reduced nicotine craving which led to decreased nicotine intake, even among those who continued smoking, as evidenced by both lower craving scores and reduced cotinine levels, a well-known metabolite of nicotine.

“More deaths each year in the U.S. are attributed to cigarette smoking than to any other preventable cause, and our current smoking cessation treatment options are limited,” said Nancy Rigotti, MD, Professor of Medicine at Harvard Medical School, Director of Tobacco Research and Treatment Center, Massachusetts General Hospital, and ORCA Program Investigator. “The study findings published today suggest that cytisinicline, if approved by the FDA, could help many smokers to quit and reduce the smoking-related risks to their health.”

Achieve plans to submit the cytisinicline New Drug Application (NDA) to the U.S. Food and Drug Administration (FDA) in June 2025.

About ORCA-3
The Phase 3 ORCA-3 trial evaluated 792 adults who smoked cigarettes daily and was conducted at 20 clinical trial locations in the U.S. The trial was initiated in January 2022 and completed enrollment in September 2022, with topline results reported in May 2023. ORCA-3 participants received 3mg cytisinicline dosed 3 times daily for either 6 or 12 weeks and were monitored through 24 weeks post randomization. The trial was blinded, placebo-controlled, and all subjects received behavioral support for the duration of the trial. The primary endpoint was biochemically verified continuous abstinence during the last four weeks of treatment. Secondary outcome measures assessed continued abstinence rates through 6 months from the start of study treatment. The full manuscript is published in *Journal of the American Medical Association (JAMA) Internal Medicine*.

About Achieve Life Sciences, Inc.
Achieve Life Sciences is a late-stage specialty pharmaceutical company committed to addressing the global smoking health and nicotine dependence epidemic through the development and commercialization of cytisinicline. The company has successfully completed two Phase 3 studies with cytisinicline for smoking cessation and one Phase 2 study with cytisinicline in vaping cessation. The company has fully enrolled its ongoing open-label safety study with cytisinicline and plans to submit its new drug application for smoking cessation in June 2025. Achieve has also conducted a successful end-of-Phase 2 meeting with the FDA for a future vaping indication.

About Cytisinicline
There are approximately 29 million adults who smoke combustible cigarettes.[1] Tobacco use is currently the leading cause of preventable death that is responsible for more than eight million deaths worldwide and nearly half a million deaths in the United States annually.[2,3] More than 87% of lung cancer deaths, 61% of all pulmonary disease deaths,

and 32% of all deaths from coronary heart disease are attributable to smoking and exposure to secondhand smoke.[3]

In addition, there are over 11 million adults in the United States who use e-cigarettes, also known as vaping.[4] In 2024, approximately 1.6 million middle and high school students in the United States reported using e-cigarettes.[5] There are no FDA-approved treatments indicated specifically as an aid to nicotine e-cigarette cessation. Cytisinicline has been granted Breakthrough Therapy designation by the FDA to address this critical need.

Cytisinicline is a plant-based alkaloid with a high binding affinity to the nicotinic acetylcholine receptor. It is believed to aid in treating nicotine addiction for smoking and e-cigarette cessation by interacting with nicotine receptors in the brain, reducing the severity of nicotine craving symptoms, and reducing the reward and satisfaction associated with nicotine products. Cytisinicline is an investigational product candidate being developed for the treatment of nicotine addiction and has not been approved by the Food and Drug Administration for any indication in the United States.

Forward Looking Statements
This press release contains forward-looking statements within the meaning of the “safe harbor” provisions of the Private Securities Litigation Reform Act of 1995, including, but not limited to, statements regarding the timing and nature of cytisinicline clinical development and regulatory review and approval, data results and commercialization activities, the potential market size for cytisinicline, the potential benefits, efficacy, safety and tolerability of cytisinicline, the development and effectiveness of new treatments, and the successful commercialization of cytisinicline. All statements other than statements of historical fact are statements that could be deemed forward-looking statements. Achieve may not actually achieve its plans or product development goals in a timely manner, if at all, or otherwise carry out its intentions or meet its expectations or projections disclosed in these forward-looking statements. These statements are based on management’s current expectations and beliefs and are subject to a number of risks, uncertainties and assumptions that could cause actual results to differ materially from those described in the forward-looking statements, including, among others, the risk that cytisinicline may not demonstrate the hypothesized or expected benefits; the risk that Achieve may not be able to obtain additional financing to fund the development and commercialization of cytisinicline; the risk that cytisinicline will not receive regulatory approval in a timely manner or at all, or be successfully commercialized; the risk that new developments in the smoking and vaping cessation landscapes require changes in business strategy or clinical development plans; the risk that Achieve’s intellectual property may not be adequately protected; general business and economic conditions; risks related to the impact on our business of macroeconomic and geopolitical conditions, including fluctuating inflation, interest and tariff rates, volatility in the debt and equity markets, actual or perceived instability in the global banking system, global health crises and pandemics and geopolitical conflict and the other factors described in the risk factors set forth in Achieve’s filings with the Securities and Exchange Commission from time to time, including Achieve’s Annual Reports on Form 10-K and Quarterly Reports on Form 10-Q. Achieve undertakes no obligation to update the forward-looking statements contained herein or to reflect events or circumstances occurring after the date hereof, other than as may be required by applicable.

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Source: Achieve Life Sciences