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Achieve Life Sciences Announces Publication of Cytisinicline Phase 3 ORCA-2 Smoking Cessation Trial in Journal of the American Medical Association (JAMA)

Cytisinicline 6- and 12-week dosing schedules, with behavioral support, demonstrated “smoking cessation efficacy and excellent tolerability”

Supports potential for cytisinicline to be the first pharmacotherapy approved for smoking cessation in nearly two decades

SEATTLE and VANCOUVER, British Columbia, July 11, 2023 (GLOBE NEWSWIRE) -- Achieve Life Sciences, Inc. (NASDAQ: ACHV), today announced the publication in [JAMA](#) of the results from the Phase 3 ORCA-2 randomized placebo-controlled clinical trial of cytisinicline as a treatment for smoking cessation, the first large trial of this medication conducted in the United States. The study authors concluded that cytisinicline demonstrated “smoking cessation efficacy and excellent tolerability” in adult smokers. ORCA-2 was the first of two Phase 3 clinical trials to report positive outcomes for cytisinicline in smoking cessation.

As reported today, the ORCA-2 trial demonstrated that biochemically confirmed continuous smoking abstinence during the last 4 weeks of treatment, the primary outcome measure, was significantly higher for cytisinicline compared with placebo for both the 6- and 12-week treatment durations. For 6-week cytisinicline treatment vs placebo, 25.3% vs 4.4% of participants were abstinent during weeks 3 to 6, and participants receiving cytisinicline treatment had 8 times higher odds, or likelihood, to have quit smoking (odds ratio (OR) 8.0 [95% CI, 3.9-16.3]; $P<.001$). For 12-week cytisinicline treatment vs placebo, 32.6% vs 7.0% of participants were abstinent during weeks 9 to 12, and participants receiving cytisinicline treatment had 6 times higher odds, or likelihood, to have quit smoking (OR 6.3 [95% CI, 3.7-11.6]; $P<.001$). Participants taking cytisinicline also had a rapid and sustained decline in cravings and smoking urges compared with placebo during the first 6 weeks of treatment.

Continuous abstinence rates were also statistically significant through 6 months, the secondary outcome measure, for both treatment durations. For 6-week cytisinicline

treatment vs placebo, 8.9% vs 2.6% of participants were abstinent during weeks 3 to 24, and participants had 4 times higher odds, or likelihood to have quit smoking (OR 3.7 [95% CI, 1.5-10.2]; P=.002). For 12-week cytisinicline treatment vs placebo, 21.1% vs 4.8% of participants were abstinent during weeks 9 to 24, and participants had 5 times higher odds, or likelihood to have quit smoking (OR 5.3 [95% CI, 2.8-11.1]; P<.001).

Participants taking cytisinicline during the entire 12 weeks of study treatment showed successful quitting beyond 6 weeks of treatment. The probability of abstinence continued to increase after week 6 in participants who received 12 weeks of cytisinicline treatment, suggesting that continued new quitting attempts occurred and were successful among participants who had not achieved complete abstinence by week 6. These findings indicate that prolonged 12-week treatment for some people who smoke may be required to achieve successful abstinence.

Rates of abnormal dreams and insomnia occurred in less than 10% of each group, and rates of headache and nausea for cytisinicline were similar to placebo rates. Only 2.9% of subjects discontinued cytisinicline due to an adverse event and no drug-related serious adverse events occurred.

“We have not seen meaningful advancements in treatment options for people who smoke – and the doctors who care for them – for nearly two decades,” said Nancy Rigotti, MD, Professor of Medicine at Harvard Medical School Director, Tobacco Research and Treatment Center, Massachusetts General Hospital, and Principal Investigator of ORCA-2. “Currently available medications do not help all smokers to quit, and they produce unacceptable side effects in others. That is why, if approved by regulators, cytisinicline could offer a new option to treat smoking, the leading preventable cause of death worldwide.”

ORCA-2 was the first of two Phase 3 clinical trials to report positive outcomes for cytisinicline efficacy and safety. The Phase 3 ORCA-3 trial, for which results were reported in May 2023, also demonstrated statistically significant cessation rates for both 6- and 12-week cytisinicline and demonstrated that cytisinicline was very well-tolerated. Based on these data, Achieve expects to submit a New Drug Application (NDA) to the U.S. Food and Drug Administration (FDA) for cytisinicline as an aid in treating nicotine dependence for smoking cessation in adults trying to quit cigarette smoking in the first half of 2024. If approved, cytisinicline would be the first FDA-approved, prescription treatment for smoking cessation available in the United States in nearly two decades.

“We believe the body of evidence to date shows that cytisinicline effectively increases cessation rates without causing troublesome side effects, which often, are a key reason patients refuse to take or continue prescription cessation medications,” said Cindy Jacobs, MD, PhD, Achieve Life Sciences President and Chief Medical Officer. “If approved by regulators, cytisinicline has the potential to become the new standard of care for the millions of people who want to quit smoking.”

About ORCA-2

The Phase 3 ORCA-2 trial evaluated 810 adults who smoked cigarettes on a daily basis at 17 clinical trial locations in the United States. The trial was initiated in October 2020 and completed enrollment in June 2021, with topline results reported in April 2022. ORCA-2 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 4 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 [JAMA](#).

About Achieve and Cytisinicline

Achieve's focus is to address the global smoking health and nicotine addiction epidemic through the development and commercialization of cytisinicline. 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.^{1,2} 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.²

In addition, there are over 11 million adults in the United States who use e-cigarettes, also known as vaping.³ In 2022, approximately 2.5 million middle and high school students in the United States reported using e-cigarettes.⁴ Currently, there are no FDA-approved treatments indicated specifically as an aid to nicotine e-cigarette cessation.

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 withdrawal 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, data results and commercialization activities, the potential market size for cytisinicline, the potential benefits, efficacy, safety and tolerability of cytisinicline, the ability to discover and develop new uses for cytisinicline, including but not limited to as an e-cigarette cessation product, and the development and effectiveness of new treatments. 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 of cytisinicline; the risk that cytisinicline will not receive regulatory approval or be successfully commercialized; the risk that new developments in the smoking cessation landscape 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 conditions, including inflation, rising interest rates, instability in the global banking sector, and public health crises, such as the COVID-19 pandemic 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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²U.S. Department of Health and Human Services. The Health Consequences of Smoking – 50 Years of Progress. A Report of the Surgeon General, 2014.

³Cornelius ME, Loretan CG, Jamal A, et al. Tobacco Product Use Among Adults – United States, 2021. MMWR Morb Mortal Wkly Rep 2023;72:475–483.

⁴Park Lee E, Ren C, Cooper M, Cornelius M, Jamal A, Cullen KA. Tobacco Product Use Among Middle and High School Students – United States, 2022. Morbidity and Mortality Weekly Report, 2022; 71:45.



Source: Achieve Life Sciences