First large US clinical trial of cytisinicline finds the smoking cessation medication effective and well tolerated

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The first large-scale U.S. clinical trial of cytisinicline, led by a Massachusetts General Hospital (MGH) investigator, found the smoking

cessation medication to be effective and well tolerated in adults who wished to break their nicotine dependence. In the Phase 3 study published in *JAMA*, researchers reported that cytisinicline could offer adults who smoke a potential new treatment option.

"Cigarette smoking remains the leading preventable cause of death worldwide, yet no new smoking cessation medication has been approved by the U.S. Food and Drug Administration for nearly two decades," says Nancy Rigotti, MD, director of MGH's Tobacco Research and Treatment Center, and lead author of the study. "There is an urgent need for new medications to treat tobacco smoking because existing products don't help all smokers to quit and can have unacceptable side effects. If approved by regulators, cytisinicline could be a valuable new option to treat tobacco dependence."

Cytisinicline (historically known as cytisine) is a naturally occurring plant-based alkaloid that binds selectively to nicotinic receptors in the brain that regulate nicotine dependence, alleviating the urge to smoke and reducing the severity of nicotine withdrawal symptoms. Its mechanism of action is similar to that of varenicline, an FDA-approved smoking cessation aid.

The 17-site randomized clinical trial, known as ORCA-2, tested cytisinicline among 810 adults who smoked cigarettes daily and wanted to quit. It is the first of two Phase 3 clinical trials conducted by Achieve Life Sciences, Inc., the drug's manufacturer.

ORCA-2 compared two durations of cytisinicline treatment—6 and 12 weeks—versus a placebo, with a follow-up to 24 weeks. The primary outcome measure was biochemically confirmed continuous smoking abstinence for the last 4 weeks of treatment. Specifically, for the 12-week group, 32.6% of participants using cytisinicline vs. 7% using placebo were abstinent during weeks 9 to 12. For the 6-week group,

abstinence was 25.3% for cytisinicline vs. 4.4% for placebo during weeks 3 to 6. Participants taking cytisinicline also experienced a rapid and sustained decline in cravings and smoking urges during the first 6 weeks of treatment.

Over the longer term, ORCA-2 found a statistically significant increase in continuous abstinence through 6 months for both treatment durations. Abstinence from weeks 9 to 24 for the 12-week group was 21.1% for cytisinicline vs. 4.8% for placebo, and for the 6-week group abstinence from weeks 3 to 24 was 8.9% for cytisinicline vs. 2.6% for placebo. Cytisinicline was also well tolerated by participants, with no serious drug-related adverse events reported and low rates of typical side effects like nausea and insomnia.

"Cytisinicline demonstrated impressive results as a smoking cessation medication in a rigorous clinical trial that used a new, scientifically-based dosing regimen as well as a longer duration of treatment than traditionally done," notes Rigotti, an internationally known expert in tobacco use and treatment. "This agent has the potential to help countless numbers of people quit smoking and, in the process, reduce the enormous toll of premature deaths and disability due to cigarette smoking in the U.S. and worldwide."

Rigotti is director of the MGH Tobacco Research and Treatment Center in the division of General Internal Medicine and Mongan Institute at MGH, and professor of Medicine at Harvard Medical School. Senior author Cindy Jacobs, Ph.D., MD, is director, president and chief medical officer for Achieve Life Sciences.

More information: Nancy A. Rigotti et al, Cytisinicline for Smoking Cessation, *JAMA* (2023). DOI: 10.1001/jama.2023.10042