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Achieve Announces Publication of Cytisine Data for Next-Generation Cytisine Molecules

SEATTLE and VANCOUVER, British Columbia, June 11, 2018 /PRNewswire/ -- Achieve Life Sciences, Inc. (NASDAQ: ACHV), a clinical-stage pharmaceutical company committed to the global development and commercialization of cytisine for smoking cessation, today announced that cytisine data, generated in collaboration with the University of Bristol, was published in *Chem*.

These data show that via the use of C-H activation chemistry, the cytisine molecule can be modified in a highly targeted and selective manner to generate a new class of cytisine derivatives that may enable future development of product candidate both for smoking cessation and other indications.

The University of Bristol strategic collaboration uses a combination of computational docking and chemical synthesis to design and generate precision chemical keys for important biological locks. Nicotinic acetylcholine receptors (nAChR) associated with acetylcholine-mediated neurotransmission have been linked to several neurological conditions and public health issues, notably tobacco addiction. The ability to design and synthesize a molecule specifically to achieve high levels of selectivity across a family of receptor subtypes is paramount for therapeutic success as poor selectivity for a particular target can be accompanied by off-target adverse effects. Molecular simulation of protein-ligand complexes was also used to understand how structural modifications might modify a ligand's activity profile. This contributes to a fundamental understanding of the mechanism of action of nAChRs but importantly also facilitates the design of accurate 'molecular keys' for better selectivity at these receptor subtypes. This, in turn, offers the potential of more precisely targeted therapies. The collaboration has modified the molecular structure of cytisine, an established nAChR partial agonist, to eliminate activation of the a7 nAChR while retaining a critical partial agonist profile at the high affinity nicotine receptor, the a4b2 nAChR subtype.

"While we believe cytisine offers an advantage over existing smoking cessation treatments, we appreciate that even low level activation of nicotinic receptor subtypes, particularly a7 nAChR, may occur and can lead to undesirable side effects," said Dr. Anthony Clarke, President & Chief Scientific Officer of Achieve. "This effort led by the University of Bristol will

enable Achieve to pursue the development of next-generation cytisine treatments, which will be highly-targeted and more potent. This offers the prospect of greater efficacy and better tolerability for newer anti-smoking medications and also the possibility of nicotinic receptor-based treatments for other indications, such as alcohol addiction and potentially opioid addiction."

Prof. Tim Gallagher, Dean of the Faculty of Science and Professor of Organic Chemistry at the University of Bristol, added, "This significant advancement is the result of a team effort across multiple academic institutions and disciplines, and was made possible through our partnership with Achieve. We can now move forward to explore the full potential of these modified cytisine ligands as therapeutic agents to help the millions of people who are battling nicotine and other addictions."

This work has involved a collaboration between groups within Chemistry and Biochemistry at Bristol, pharmacologists and neuroscientists at University of Bath, Oxford Brookes University and the University of Milan, and Achieve Life Sciences.

The full publication, *Unlocking Nicotinic Selectivity via Direct C–H Functionalization of (−)-Cytisine*, is available via Open Access and can be viewed at https://doi.org/10.1016/j.chempr.2018.05.007.

About Achieve & Cytisine
Achieve's focus is to address the global smoking health epidemic through the development and commercialization of cytisine. Tobacco use is currently the leading cause of preventable death and is responsible for nearly six million deaths annually worldwide[1]. It is estimated that 28.6% of all cancer deaths in the U.S. are attributable to cigarette smoking[2].

Cytisine is a plant-based alkaloid with a high binding affinity to the nicotinic acetylcholine receptor. Two prior, large-scale Phase 3 clinical studies of cytisine, with favorable outcomes, have been successfully completed in over 2,000 patients. The TASC trial was a 740 patient, double-blind, placebo controlled trial conceived by Professor Robert West at University College London and funded by the U.K. National Prevention Research Initiative. The CASCAID trial was a 1,310 patient, single-blind, non-inferiority trial comparing cytisine to nicotine replacement therapy (NRT). The CASCAID trial was conceived by Dr. Natalie Walker, National Institute for Health Innovation, University of Auckland and funded by the Health Research Council of New Zealand. Both trials were published in the New England Journal of Medicine.

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 potential benefits of cytisine. 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 cytisine 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 cytisine; the risk that cytisine 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; 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 law.

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[1] World Health Organization. WHO Report on the Global Tobacco Epidemic, 2011, Geneva: World Health Organization, 2011.
[2] Annals of Epidemiology , Volume 25 , Issue 3 , 179 - 182.e1