at a glance™

ACHIEVE LIFE SCIENCES

Highlights: ***A multi-center Phase 2b clinical trial of Achieve Life Sciences' naturally-sourced smoking cessation agent, cytisinicline, will report top line results the end of the second quarter. The pivotal Phase 3 program is scheduled to start 2H19. Two prior studies show cytisinicline has similar quit rates (22-percent at six months) as shown for category-leading Chantix®, but with a shorter treatment period (25 days vs. 12 weeks), and a more favorable adverse event profile.***

Key Considerations

- **The roughly $1.2 billion global market for prescription smoking cessation drugs needs an alternative to Chantix, currently the leading product.**
- **Chantix produced a roughly 22-percent quit rate at six months after 12 weeks of treatment, including standard behavioral support, in an 8,000-patient study conducted by Pfizer. Treatment-limiting side effects included sleep disturbance, nausea and vomiting, nightmares, and headache.**
- **In a separate investigator-led 1,350-patient study published in the *New England Journal of Medicine*, Achieve's candidate, cytisinicline (pronounced *site-a-sin-a-cline*, and known outside the US as cytisine), also demonstrated a 22-percent quit rate at six months after only 25 days of treatment.**
- **The two-thirds shorter treatment period, coupled with a favorable safety profile versus Chantix, are expected to give cytisinicline the necessary competitive features for early adoption, rapid growth, and leadership in a $1 billion-plus category.**
- **Both Chantix and cytisinicline are formulated as oral pills.**
- **Achieve licensed global rights (except Central and Eastern Europe) to cytisinicline from Bulgaria-based Sopharma, which has been marketing the naturally-sourced product for smoking cessation for the past 20 years. More than 20 million smokers have used the product as an aid to quit smoking.**
- **Although it has been popular in Sopharma's home territories, cytisinicline/cytisine has never been marketed elsewhere and has never been tested for government-approved use in the US or in any other major market.**
- **Achieve's primary focus is to conduct registration-directed clinical trials for FDA approval and enter the $800 million US market created by Chantix.**
- **A pivotal Phase 3 trial is planned to begin in 2H19 following top-line results from a 25-day Phase 2b trial in June. The last study visit for the last subject in the 254-patient Phase 2b trial was announced April 24, 2019.**
- **Several patent families are being pursued globally, including formulation, method of use and extraction. A patent was recently issued on a new cytisinicline salt formation. Various government regulations give the molecule exclusivity for five years in the US and for 10 years in EU countries where it is not already approved.**
- **The University of Bristol (UK) is working with Achieve on possible indications for cytisinicline derivatives in alcohol and opioid addiction.**

Achieve Life Sciences, Inc.

(Nasdaq: ACHV)

Recent Price:	**$4.35**
Approx. Shares O/S:	**6.7 Million**
Approx. Mkt Cap:	**$29 Million**
Fiscal Year Ends:	**December 31**

Published: April 2019

Smoking Cessation Market

The world, including America, still smokes. There are 36 million adult smokers in the US; globally, the number is roughly 1.1 billion.

Five hundred thousand Americans die each year from smoking-related disease. Smoking is implicated in 30 percent of all cancers, and it's the dominate cause (87 percent) of lung cancers. Smoking-related illness in the US costs over $300 billion a year, including nearly $170 billion in direct medical care for adults, and $156 billion in lost productivity.

Those who seek to kick the habit spend roughly $16 billion annually on smoking cessation aids, mainly nicotine replacement therapy such as gums and patches which are now widely available over-the-counter.

It is estimated that more people are addicted to nicotine than any other drug.

Seventy-seven percent of smokers desire to quit and more than half attempt to quit each year. Despite the high number of multiple attempts, only about 4 to 7 percent of smokers are successful in quitting, and they commonly switch between products and different behavioral modification approaches to do so.

The dominant prescription product is Chantix, which sells roughly $800 annually in the US and another $250 million internationally.

The payer landscape in the US is favorable with most insurance plans covering multiple quit attempts per year, including prescription and over-the-counter medications.

For all its drawbacks, Chantix is the leading comparator in terms of quit rates at six months. Achieve believes it can take market share away from Chantix, and possibly grow the category, by providing a prescription smoking cessation aid that is comparable to Chantix's quit rates but requires a shorter treatment period and has fewer side effects.

Two investigator-led Phase 3 trials of cytisinicline in more than 2,000 patients have been published in the *New England Journal of Medicine*. Both demonstrated superior quit rates to nicotine replacement therapy and to placebo and confirmed cytisinicline's favorable safety profile.

The first trial, called TASC, enrolled 740 patients under a double-blind, placebo-controlled protocol. The data showed that cytisinicline was 3.4 times more likely to result in smoking cessation at 12 months versus placebo.

The second large trial, called CASCAID, enrolled 1,310 patients and produced a

Notable & Upcoming Milestones

1Q19 – Top-line results reported of Ph 1/2 repeat-dose PK/PD study

1Q19 – Enrollment completed in 254-subject Phase 2b

Mid-19 – Top-line results of Ph 2b expected

2H19 – Start of pivotal Ph 3

cytisinicline quit rate of 22-percent at six months. This is the same quit rate achieved by Chantix in the 8,000-patient EAGLES trial Pfizer conducted to overcome a black box warning.

As part of the agreed FDA registration process, the FDA asked Achieve to compare the standard 1.5mg dose to a higher 3mg dose.

A small study showed a higher quit rate with the higher dose; however, the speed in reducing the number of cigarettes smoked and the safety profile remained essentially the same for each group.

Smoker Stats

36 million US adult smokers
77% desire to quit
55% attempted in past year
4% to 7% succeeded
8 to 11 estimated attempts before quitting permanently

Patients who enrolled in the two groups of the study smoked an average of 17 cigarettes a day. Within 48 hours of starting treatment with cytisinicline, the number of cigarettes smoked by subjects in both groups dropped by an average of 75 percent. This suggests cytisinicline works quickly. The Phase 2b and Phase 3 studies are expected to validate this further.

About Cytisinicline (*site-a-sin-a-cline*)

So, where did cytisinicline come from? Achieve found cytisinicline in Bulgaria. It's been marketed by a company called Sopharma for over 20 years, with a safety database now totaling more than 15 million patients. Sopharma has not sought approval outside of Central and Eastern Europe.

Cytisinicline has a well-established dual-acting mechanism. It binds to the α4β2 receptor and acts as both an agonist (stimulator) and an antagonist (blocker), an ideal combination for smokers seeking to quit.

As an agonist, cytisinicline partially stimulates dopamine release. This helps compensate for the reduction in nicotine stimulation, reducing overall nicotine craving and the severity of withdrawal symptoms.

As a partial antagonist, cytisinicline blocks the binding of nicotine to the receptor. This removes the nicotine-induced reward and satisfaction associated with smoking.

Cytisinicline also reduces the number of α4β2 receptors that would typically be present in a smoker, further reducing the craving for nicotine.

Because cytisinicline is highly targeted to the α4β2 receptor it has very little off-target activity, whereas Chantix activates the α7 and 5-HT3 receptors, among others, which are believed to be responsible for sleep issues, headaches, and the nausea and vomiting commonly associated with Chantix.

In a meta-analysis of multiple cytisinicline and Chantix clinical trials, the incidence of sleep disorders and abnormal dreams was five times greater in subjects treated with Chantix versus cytisinicline (12.5 percent versus 2.5 percent). The incidence of nausea and vomiting occurred nearly seven times more frequently (27.8 percent versus 4.1 percent), and headache was reported by 12.7 percent of subjects on Chantix versus 1.4 percent of those on cytisinicline.

A recently completed Phase 1/2 PK/PD study evaluated the repeat-dose effects of 1.5 mg and 3.0 mg cytisinicline in 26 healthy volunteer smokers over the standard 25-day course of treatment. Cytisinicline was well tolerated with only transient, mild-to-moderate headache as the most common adverse event, which was not treatment limiting.

The PK results showed expected increases in plasma concentration between the standard 1.5 mg and 3.0 mg doses of cytisinicline but no evidence of drug accumulation. By day 26, subjects had an average 80 percent reduction in cigarettes smoked. Biochemically verified smoking cessation rates were 39 percent and 54 percent in the 1.5 mg and 3.0 mg cytisinicline treated groups, respectively.

Last Step before Phase 3

The final step before starting the Phase 3 pivotal trial program of cytisinicline for smoking cessation is the completion and reporting of a double-blind, placebo-controlled 25-day Phase 2b optimization study.

The study will compare placebo to two different strengths of cytisinicline (1.5mg and 3mg) using two different dosing protocols, a 25-day titration schedule and a three-times-daily schedule for 25 days.

The Phase 2b started in 4Q18. Enrollment was completed in February 2019. Top line results are due mid-2019.

Two hundred fifty-four subjects who smoke approximately 10 cigarettes a day and who had greater than 10 parts per million of carbon monoxide in expired air were enrolled. They were randomized 1:1 to either of the two different dosing schedules.

All patients receive standardized behavioral support. The primary endpoint will be the number of cigarettes smoked during the 25-day study period.

About the Founders

Richard Stewart, CEO, and Anthony Clarke, PhD, CSO, formed Achieve Life Sciences in 2015 and licensed the global rights (ex-Central and Eastern Europe) to cytisinicline. In August 2017, the company reverse-merged with Oncogenex, principally to provide a strong management team with excellence in clinical trials and in regulatory, financial and commercial operations.

Mr. Stewart and Dr. Clarke also founded Brabant Pharma which was sold to Zogenix, Inc. (ZGNX) in 2014. Zogenix recently completed the second successful Phase 3 in Dravet syndrome, a rare form of intractable epilepsy that begins in infancy. Stewart and Clarke founded Huxley Pharmaceuticals which was sold to BioMarin (BMRN), and Amarin Corporation (AMRN) which recently completed a successful Phase 3 triglyceride program. Mr. Stewart's very first company, SkyePharma, was sold to UK-based Vectura Group (GBX).

Summary

- **Achieve is conducting late-stage registration-directed clinical trials for a prescription smoking cessation aid that takes direct aim at Chantix's billion-dollar franchise.**
- **A pivotal Phase 3 trial program is set to begin in the 2H19, following top-line results from a Phase 2b trial at the end of the second quarter.**
- **Achieve's naturally-sourced active ingredient, cytisinicline, produces quit rates at six months that are equal to those reported for Chantix. Cytisinicline has demonstrated a more tolerable safety profile, and requires a substantially shorter treatment period – 25 days versus 12 weeks for Chantix.**
- **Cytisinicline has a registered safety data base that currently includes more than 15 million users.**
- **Achieve's two founders have been instrumental as founders and key managers in three pharma companies sold at premium valuations, and a fourth, Amarin, that remains independent with a market cap of approximately $6.3 billion.**
- **Achieve's cash/cash equivalents at December 31, 2018 totaled $14.7 million.**

For additional information, contact:
Redington, Inc. • CT 203 222-7399 • NY 212 926-1733 • www.redingtoninc.com
Achieve Life Sciences, Inc. • 425 686-1500 • www.achievelifesciences.com