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Achieve Life Sciences, Inc. (ACHV - NASDAQ)

A Reason to Quit is a Reason to Buy

Based on our DCF model and a 15% discount rate, ACHV is valued at approximately $6.00 per share. Our model applies a 15% probability of eventual cytisinicline sales based on historical Phase II trial success ratios. Our valuation includes geographic contributions from the United States only.

Current Price (3/1/2019)	$2.45
Valuation	**$6.00**

INITIATION

Achieve Life Sciences is developing cytisinicline for use as a smoking cessation treatment for approval and commercialization in the United States and RoW. The candidate is currently in a Ph2b optimization clinical trial which is expected to read out in mid-2019.

Two Ph3 studies are planned in up to 2,300 patients with the first starting in late 2019 and the second in first half 2020. The trials will compare cytisinicline with placebo combined with counseling. The primary endpoint is abstinence at two months with follow-up to six months.

Current products on the market have only limited effectiveness and come with unpleasant side effects including nausea, vivid dreams, insomnia and GI issues. Cytisinicline may fill a void in the prescription and NRT market by reducing nicotine cravings, the severity of withdrawal and the reward associated with smoking along with fewer side effects and shorter treatment duration. There are almost 40 million smokers in the US and over 1 billion globally, providing a substantial population demanding an improved smoking cessation product.

ACHV holds sufficient capital to complete the Ph2b but will require additional capital to complete Ph3 studies. Based on our assessment of market penetration, we initiate with a target price of $6.00 per share.

SUMMARY DATA

52-Week High	**15.10**
52-Week Low	**1.04**
One-Year Return (%)	**-80.7**
Beta	**2.38**
Average Daily Volume (sh)	**1,398,570**
Shares Outstanding (mil)	**6.7**
Market Capitalization ($mil)	**16.5**
Short Interest Ratio (days)	**2.1**
Institutional Ownership (%)	**26.7**
Insider Ownership (%)	**5.0**
Annual Cash Dividend	**$0.00**
Dividend Yield (%)	**0.00**
5-Yr. Historical Growth Rates	
Sales (%)	**N/A**
Earnings Per Share (%)	**N/A**
Dividend (%)	**N/A**
P/E using TTM EPS	**N/A**
P/E using 2017 Estimate	**N/A**
P/E using 2018 Estimate	**N/A**
Zacks Rank	**N/A**

Risk Level	**Above Average**
Type of Stock	**Small-Growth**
Industry	**Med-Biomed/Gene**

ZACKS ESTIMATES

Revenue

(In millions of US$)

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2017	$0.0 A	$0.0 A	$0.0 A	$0.0 A	$0.0 A
2018	$0.0 A	$0.0 A	$0.0 A	$0.0 E	$0.0 E
2019					$0.0 E
2020					$0.0 E

Earnings per Share

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2017	-$96.56 A	-$78.19 A	-$8.96 A	-$3.14 A	-$22.07 A
2018	-$2.43 A	-$1.82 A	-$0.71 A	-$0.50 E	-$3.54 E
2019					-$1.01 E
2020					-$1.16 E

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INITIATING COVERAGE

Achieve Life Sciences, Inc. (NASDAQ: ACHV) is developing cytisinicline, historically known as cytisine, for nicotine addiction. The drug is currently available over the counter (OTC) in several eastern European countries for this indication and has been successful with annual revenues in excess of $20 million there; however, it is not approved by the FDA or EMA. Achieve has licensed cytisinicline for development and commercialization in the United States and most other geographies around the world including parts of Europe, the Middle East, Africa and Asia. The drug formulation has been used by over 20 million smokers in Central and Eastern Europe for smoking cessation and also in over 2,000 subjects in previously conducted investigator-led Phase 3 clinical trials. Given the clinical and in-market data available, the safety and efficacy profile are well characterized and provide a degree of confidence that successful regulatory trials can be conducted for FDA approval.

Cytisinicline is an attractive alternative to current smoking cessation products and in comparisons conducted by the Cochrane Group, has shown similar efficacy to Pfizer's Chantix, the current leading prescription product, and may provide an improved safety and side effect profile. Prescription treatments also show greater success in stopping smoking as compared to over-the-counter patches, gums and lozenges.

There are approximately 1 billion smokers in the world, with an estimated 40% attempting to quit annually. Solutions available to this group include prescription only drugs such as Chantix (varenicline) and Zyban (bupropion) plus nicotine replacement therapies (NRTs) such as patches, gums and lozenges. Behavioral therapies and counseling are also important non-drug treatments that can be used independently and more successfully in conjunction with medication. While the current paradigm of treatment does help some individuals, success rates are low and only about five to six percent per year stop smoking after an attempt to do so. According to the Center for Disease Control (CDC) it can take 8-11 quit attempts before success. The highly addictive nature of nicotine, social influences, adverse effects associated with NRT and non-nicotine medications, and other factors are faulted for the low success rate.

The single most beneficial action a smoker can take to improve their own and surrounding family's health is to stop smoking. Approximately 30% of all cancers and up to 87% of lung cancer is caused by the addictive habit. Additional diseases associated with smoking include cardiovascular and respiratory disease, diabetes and macular degeneration. Despite the damage caused by this vexing habit, nicotine is highly addictive and quitting is very difficult. Nicotine addiction can be as strong as other addictive substances such as heroin and cocaine.[1] The effect on health and health care costs of the estimated greater than one billion persons smoking in the world is estimated to be $1 trillion annually with over $300 billion in the U.S.[2]

With a serious health risk from smoking and only modest benefit from existing treatments, it is clear that an unmet need exists. Introducing cytisinicline beyond Eastern Europe may provide an additional tool for smokers who have failed using other approaches and provide a product with a potentially improved side effect profile and shorter duration of treatment. Cytisinicline may present fewer incidences of nausea, vomiting, sleep disorders, insomnia and headache as compared to its most direct competitor, Chantix. With the completion of successful clinical trials, we see cytisinicline as a potential solution for the high unmet need in this space with potentially similar efficacy to Chantix and greater efficacy over NRT and antidepressant medications (such as bupropion) and improved side effect profile compared to Chantix.

Achieve currently holds one development product in its portfolio, cytisinicline, which is currently in preparation for two Phase III trials. The first trial is anticipated to be an 800 person study with two arms (1.5 mg versus placebo) which will start before year end 2019 and will last for approximately one year. The second (1.5 mg, 3.0 mg versus placebo) is a 1,500 person three-arm study starting first half 2020 and lasting for approximately 18 months. Following the anticipated favorable results from the two studies, we anticipate a submission of an NDA to the FDA in early 2022.

[1] https://drugwarfacts.org/chapter/addictive_properties#sthash.OUgShqm1.dpbs
[2] World Health Organization and Centers for Disease Control and Prevention estimates.

The company held $13.1 million in cash and equivalents on its balance sheet as of September 30, 2018 and subsequent to the quarter end raised an additional net $5 million. Based on forecasted cash burn rates, we anticipate a cash balance of approximately $15 million at year end, which should support operations for the next two or three quarters. However, management has made clear they will require additional capital prior to the start of the Phase III trials and we anticipate this to take place in the Q2/Q3 2019 timeframe and after additional analysis of Phase IIb data. As the Phase III trials advance over the next two years, we forecast an acceleration in cash burn. Capital requirement may be mitigated from commercial partnering activities in the U.S. and elsewhere.

The low rates of success with current smoking cessation therapy and the high rates of side effects for varenicline and bupropion create an unmet need that cytisinicline may partially address. Cytisinicline may be able to show impressive quit rates when combined with behavioral support and a lower side effect profile compared to current market leader varenicline to penetrate a medication market of near $5 billion. We initiate on the shares of Achieve Life Sciences with a target price of $6.00.

INVESTMENT THESIS

Smoking is one of the most pervasive and preventable health issues faced today. Over one billion or about 20% of people smoke worldwide and almost 40 million or 15% smoke in the United States. The CDC estimates that about 70% of these individuals want to quit and over 50% have attempted to quit in the US. However, one of the components in tobacco, nicotine, is highly addictive, making the effort to stop smoking very difficult. There are many good reasons to quit with lung and other types of cancer, heart disease, stroke and pulmonary diseases all advanced by smoking. The CDC also estimates smoking reduces lifespan by about 13 years for men and 14 years for women, which is in addition to a lower quality of life during the later years.

One popular method to stop smoking in recent years is the use of e-cigarettes, or vaping, which deliver liquid nicotine into a mist or vapor which is inhaled. This method of consumption avoids the chemicals that are associated with smoke, but e-cigarettes are not FDA approved and may have other health and safety issues associated with them. The FDA considers e-cigarette use as an epidemic particularly in youth with almost 5 million juveniles using e-cigarettes during 2018, an increase of 78% over the prior year.[3] While not exposed to the chemicals in smoke, the e-cigarette user remains addicted to nicotine and is exposed to other chemicals with undetermined side effects. Other approaches to smoking cessation include nicotine gum, patches, lozenges, sprays and inhalers. Prescription medications are other methods and include Zyban and Chantix. The currently approved products have varying rates of success and adverse effects that can limit effectiveness. 2018 sales of NRT and smoking cessation medication is approximately $4.6 billion.[4] Chantix alone had global revenues of $1.1 billion in 2018, a, 8.7% increase from 2017, of which 76% came from the U.S. market.

Cytisinicline is a smoking cessation product that has been used in Central and Eastern Europe since the 1960s and is a natural extract from the *Cytisus Laburnum* plant. Cytisinicline provides a pharmacological action similar to nicotine that helps with the cravings and withdrawal symptoms associated with quitting smoking. The compound has been examined in several investigator-led Phase III studies and has been used by over 20 million smokers. The wide use of the molecule and well-understood safety profile provide confidence that it can show sufficient efficacy and safety to obtain FDA approval following successful conclusion of the two required Phase III studies. The FDA considers cytisinicline to be a New Chemical Entity (NCE) because it has never been approved in the U.S.

Achieve has a license and supply agreement with partner Sopharma to provide support on development and manufacturing as well as an exclusive supply of cytisinicline. While cytisinicline is considered a natural product and cannot be patented, a successful approval from the FDA will provide five years of exclusivity for the product in the US and ten years in EU countries. Additionally, a novel salt-form of cytisinicline has been patented which could provide future protections for the product beyond the regulatory exclusivity periods. An improved product offered to a large global population that is trying to quit provides an attractive market for Achieve Life Sciences, especially given there have been no new smoking cessation treatments in over a decade. With over half of the population of smokers trying to quit, we estimate there will be about 25 million Americans and several hundred million individuals globally in the addressable market when cytisinicline is approved.

[3] Youth Tobacco Use: Results from the National Youth Tobacco Survey
https://www.fda.gov/TobaccoProducts/PublicHealthEducation/ProtectingKidsfromTobacco/ucm405173.htm
[4] Coherent Market Insights Global Smoking Cessation and Nicotine De-addiction Products Market Overview.

Key reasons to own ACHV shares:

- **Proven asset with use in over 20 million smokers**
- **Preliminary data shows improved efficacy and favorable side effect profile vs. current products**
- **Shorter therapy duration vs. other NRT or Chantix**
- **Dual acting MoA reduces cravings, withdrawal symptoms & prevents rush from smoking**
- **Previous Phase III studies completed in over 2,000 subjects demonstrate safety and efficiacy**
- **Pursuing smoking population of ~40 million in US and over one billion worldwide**
- **Smoking cessation medication market value of $4.6 billion in 2018**
- **Company maintains sufficient cash to complete currently active trials**

In the following sections we estimate the number of smokers worldwide and review the addictive nature of cigarettes. We then examine the hazards of cigarette smoke on health and its association with some of the most common diseases that occur today. Next is a summary of competing products as well as their benefits and shortcomings. Cytisinicline is introduced along with its history and mechanism of action (MoA) followed by a discussion of clinical trials that have taken place to evaluate the drug and future trials that will be sponsored by the company. Finally, we review Achieve's financial performance, partners and management team, evaluating strengths and weaknesses. Our evaluation is concluded with an analysis of the market potential for cytisinicline under Achieve's control and a discussion of the valuation parameters and price target. With favorable outcomes expected from the upcoming Phase III trials, we anticipate a successful 2023 launch of the product. Our valuation, generates a target price of $6.00 per share.

Nicotine Addiction

For I hate, yet love thee, so,
That, whichever thing I show,
The plain truth will seem to be
A constrained hyperbole,
And the passion to proceed
More from a mistress than a weed.

Charles Lamb, A Farewell to Tobacco (1805).

How Prevalent is Tobacco Smoking?

The National Institute for Health (NIH) and the World Health Organization (WHO) estimate that there are 1.1 billion smokers in the world[5] and almost 40 million[6] in the United States. There are 6.3 million deaths from cigarette smoking for primary users and almost 900,000 for those exposed to secondhand smoke.[7] Countries with the highest rates of smoking include Belarus, Russia, Greece and China. China is also the most populous nation with over 300 million individuals craving a cigarette puff according to the WHO. The problem is particularly prevalent in developing countries which lack strict smoking laws and may have governments that rely on tax revenues generated from the industry. Smoking is associated with a range of diseases including multiple types of cancer, emphysema, heart disease, increased risk of blindness and decline in mental function among other maladies. The U.S. Centers for Disease Control and Prevention say that smokers shorten their lives by 13 to 15 years compared to non-smokers.

Nicotine Addiction

Smoking is difficult to quit due to the addictive nature of nicotine. Nicotine is a component of tobacco and is carried to the smoker's lungs when they inhale the smoke. It enters the bloodstream through the lungs and disperses throughout the body providing pleasant physical and mood altering effects. Within seconds of inhaling tobacco smoke, nicotine will reach the brain. The toxic alkaloid stimulates the release of neurotransmitters including acetylcholine, beta-endorphin, dopamine, norepinephrine, serotonin, vasopressin, arginine and ACTH. This causes vasoconstriction, tachycardia and increased blood pressure in the body. The smoker feels enhanced pleasure, decreased anxiety, and a state of alert relaxation. The drug's profile changes from stimulant to sedative in increasing dosages and use. Nicotine addiction promotes drug-reinforced behavior, compulsive use, and frequent relapse following abstinence.

Drug addiction begins by building a tolerance in the body and brain. As exposure levels of a drug, including nicotine, are increased over time, tolerance builds up in the system and greater levels of nicotine are required to achieve the same effect. The nicotine from cigarettes is absorbed through the lungs and into the bloodstream, then carried through to the brain where the molecules attach to acetylcholine receptors. This has an immediate effect on breathing and heart rate, along with memory and ability to learn. Binding of nicotine to the acetylcholine receptors stimulates production of dopamine, a neurotransmitter associated with pleasure and reward. The feeling of pleasure and reward is the mechanism that draws smokers back to that next cigarette.

<u>Source of Nicotine</u>

Nicotine is an alkaloid, fat soluble molecule that naturally comes from plants in the nightshade family. The most common source is *Nicotiana tabacum*, or the tobacco plant which is grown globally, particularly in China, India and Brazil. The chemical compound is an oily liquid that will mix with water and has a boiling point of 247 °C. Nicotine will burn at a temperature below its boiling point, and its vapors will combust at 35 °C in air despite a low vapor pressure. As a result, most of the nicotine is burned when a cigarette is smoked; however, enough is inhaled to provide the desired effects. When exposed to heat, a portion of the nicotine vaporizes and the rest is transferred to the small airways and alveoli of the lung. The drug is dissolved and transferred across cell membranes at a rate dependent on pH to reach the bloodstream then the brain.

[5] The Society of Thoracic Surgeons
[6] Centers for Disease Control and Prevention. Current Cigarette Smoking Among Adults—United States, 2016. Morbidity and Mortality Weekly Report 2018;67(2):53-9 [accessed 2018 Feb 22].
[7] Global Burden of Disease Collaborative Network. Global Burden of Disease Study 2016 (GBD 2016) Results. Seattle, United States: Institute for Health Metrics and Evaluation (IHME), 2017.

Exhibit I – Tobacco Plants[8]

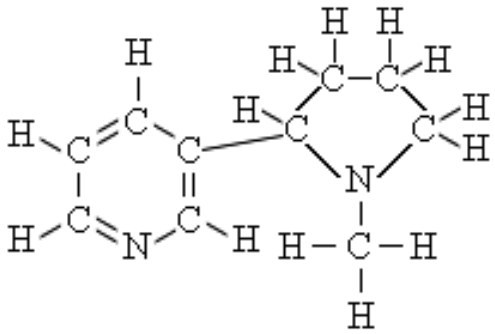


Nicotine Mechanism of Action

Nicotine acts as an agonist on nicotinic acetylcholine receptors (nAChRs) which are found throughout the body, autonomic ganglia, at neuromuscular junctions, in the adrenal medulla and the brain. The receptors are also located on the pre-synaptic axon terminals of the central nervous system. This action facilitates neurotransmitter release and thereby mediates the complex actions of nicotine in tobacco users.

Neurotransmitters are released when nicotine acts on receptors. These include dopamine, glutamate, acetylcholine and gamma aminobutyric acid. These have short term euphoric effects such as pleasure, increased attention and mental processing ability and improved working memory. Nicotine binds to nAChRs located in muscles and in the ventral tegmental area of the brain. As the stimulant interacts with the receptors, this causes release of dopamine in the nucleus accumbens providing the sense of pleasure that the smoker seeks. Nicotine interferes with the normal binding of acetylcholine, which is an important neurotransmitter and increases the level of activity with the nAChRs. This increase in activity creates an imbalance which triggers a reaction to reduce the production of acetylcholine. Over time, the receptors become desensitized and the number of receptors increases in response to constant nicotine exposure.[9] As the number of receptors increase, this creates tolerance and higher levels of nicotine are required to achieve the same effect.

Exhibit II – Nicotine Chemical Structure ($C_{10}H_{14}N_2$)



[8] By Derek Ramsey / derekramsey.com, CC BY-SA 4.0, https://commons.wikimedia.org/w/index.php?curid=1397609
[9] Govind, AP, et al. Nicotine-induced upregulation of nicotinic receptors: underlying mechanisms and relevance to nicotine addiction. Biochem Pharmacol. 2009 Oct 1;78(7):756-65.

When an individual stops smoking, the receptors are not activated due to the absence of nicotine and the pleasure response ceases. This causes withdrawal symptoms including severe cravings, irritability, anxiety, anger, poor concentration, restlessness, impatience, increased appetite, weight gain and insomnia. The brain receptors are also accustomed to stimulation by nicotine in certain situations such as while drinking or after a meal, which can also cause craving for a cigarette when an individual is in one of these settings.

Hazards of Smoking

Smoking cessation is the single most helpful action a smoker can take to improve their health. According to the CDC, cigarette smoking causes more than 480,000 deaths in the United States and is implicated in 90% of all lung cancer deaths and 80% of deaths from chronic obstructive pulmonary disease (COPD). Smokers are also at a greater risk of cardiovascular disease due to the effect chemicals in smoke have on the endothelial cells that line blood vessels. These cells can become swollen and inflamed, thereby narrowing the blood vessels and restricting blood flow and encouraging the formation of plaque.

There are approximately 4,000 chemical compounds[10] in tobacco smoke, many of which are associated with a variety of cancers. Some of these carcinogens include formaldehyde, arsenic, ammonia and benzene. According to the American Cancer Society, about half of deaths from twelve cancer types are attributable to cigarette smoking, including cancers of the liver, colon & rectum, lung, oral cavity & throat, esophagus, larynx, stomach, pancreas, bladder, kidney, cervix and acute myeloid leukemia. The chemicals can also damage the tissue in the lungs by attaching to the alveoli and entering the bloodstream.

Smoking is also associated with early delivery for pregnant mothers, reduced fertility, osteoporosis, macular degeneration, rheumatoid arthritis and decreased immune function.

There is a greater risk for those who smoke later in life. Individuals who smoke in their 50s and later are at 10 times more risk than those who stop before age 40. Discontinuing the habit before age 40 can avoid more than 90% of the excess mortality associated with smoking and 97% of this risk can be avoided by stopping before age 30.[11] Quitting smoking can reduce the risk of heart attack, stroke and a broad variety of cancers. Halting the use of cigarettes also leads to an improvement in lung function and after 15 years of not smoking, an individual's risk of coronary heart disease is the same as a non-smoker.

Smoking Cessation Therapies

Despite the large population of smokers throughout the world, many in this group realize the health risks and want to quit. However, the highly addictive nature of nicotine prevents them from being successful. A Center for Disease Control study found that almost 70% of smokers want to quit, over half have tried to quit, but only 6% were able to kick the habit. By the time cytisinicline is approved, we see an addressable market of near 25 million who are actively trying to stop. With only one in five people remaining abstinent at 6 months using most efficacious therapy and the high long-term failure rate of almost 90% for existing therapies, there is a material unmet need for new solutions.

Nicotine Replacement Therapies (NRTs)

Although the harm from smoking is associated with the smoke, it is the nicotine that produces the pharmacological effects that lead to addiction. Nicotine replacement products include a variety of administration types to replace the nicotine that is lost when a patient stops smoking. They can include patches, gums, lozenges, sprays, inhalers and tablets and are most commonly used in an attempt to quit smoking. NRT does not precisely reproduce the exposure of arterial nicotine absorbed in the body through smoking, resulting in some symptoms of withdrawal. While smoking can deliver nicotine to the brain in seconds, NRT approaches can take many minutes or hours to achieve the same effect and the user can suffer withdrawal symptoms during the delay. Despite the imperfect mechanism, the low cost and ease of use are primary reasons why these solutions are used. All of these products are available OTC, except for the nasal spray and inhaler, and can be purchased for around $50 for a month of treatment. NRT therapy[12] is expected to last from two to six months, providing a period to taper off the desire for nicotine.

[10] Nordqvist, C., What Chemicals Are In Cigarette Smoke? July 13, 2015. https://www.medicalnewstoday.com/articles/215420.php See link for a representative listing of identified compounds.
[11] Pirie, K., et al. The 21st century hazards of smoking and benefits of stopping: a prospective study of one million women in the UK. Lancet. 2013 Jan 12; 381(9861): 133–141.
[12] https://freedomfromsmoking.org/static/pdfs/FFS_Medication_Chart_Download.pdf

Electronic cigarettes are another approach used for nicotine replacement but are not approved by the FDA. These devices include a system that either vaporizes or nebulizes liquid sealed in a cartridge. The liquid contains glycerol, propylene glycol, water, nicotine and flavors. There are concerns with e-cigarettes regarding labeled and measured nicotine content and there is insufficient information of the effect of the vaporized liquid and whether or not it may be harmful. Although the market for e-cigarettes is large, we do not categorize this as a cessation therapy or competitor, especially for patients trying to eliminate their addiction.

Side Effects and Contraindications

There are a number of common side effects associated with nicotine replacement therapies (NRTs) with most related to the method of administration. The gum and lozenge can cause mouth sores, dry mouth, coughing, indigestion and jaw ache, while the patch can result in skin irritation and insomnia. The inhaler and spray can also cause irritation of the throat, mouth and nose and can cause coughing. Overall, side effects are mild, but sometimes can be serious and there have been incidence of fires and explosions for electronic cigarettes.

Prescribed Medications

Chantix (varenicline)

Initial development of varenicline was inspired by cytisine. Pfizer closely studied the *Laburnum anagyroides* plant and its chemical derivative cytisine during the 1990s to create a synthetic drug which could be patented. Varenicline was eventually approved in 2006 and achieved sales of almost $850 million in 2008, after which they declined due to safety concerns related to alleged increase suicide rates in patients. Quit rates have ranged from 14 to 44% in a variety of studies, and in many randomized, placebo-controlled comparisons, varenicline has shown statistically significant and better efficacy than placebo. However, other research has shown no meaningful difference between the drug and NRT therapy.[13] Additionally, the highest cited quit rate was at the end of the 12 week treatment period, rather than at six months, the latter of which is more indicative of long-term success. This impressive quit rate was accompanied by ~25 counseling sessions which may not be a component of real-world therapy. Shortly after varenicline was approved, there were complaints of suicidality and neuropsychiatric events which led to a black box warning being added to the label. After several years and the 3-year EAGLES trial, the black box was removed in December 2016; however, concerns may remain regarding the drug's side effect profile.

Similar to cytisinicline, varenicline is a partial agonist for the $\alpha_4\beta_2$ nAChR subtype, preventing the binding of nicotine. Blocking the ability of nicotine to activate the receptor prevents stimulation of the mesolimbic dopamine reward system. It also partially activates the nAChRs which provides nicotine-like effects and prevents withdrawal. It has been found to be more effective than NRT, but with more adverse effects and a higher cost.

The course of therapy for varenicline is 12 weeks, which is followed by another 12 weeks of therapy for those who have successfully stopped smoking to reinforce long-term abstinence. Additional studies have shown improved success when varenicline is combined with NRT therapy or counseling.

Varenicline comes in two strengths, a 0.5 mg form and a 1.0 mg form. The 0.5 mg pill is taken once per day for the first three days, then twice per day for the next four days. Two 1.0 mg pills are taken daily from day eight until the end of treatment.

Side Effects and Contraindications

About a third of patients using varenicline suffer mild to moderate nausea. Other side effects include headache, difficulty sleeping and nightmares. Following varenicline approval, some patients reported thoughts of suicide and suicidal behavior and erratic behavior, which led to a black box warning requiring use to be discontinued if these effects were observed. However, an additional clinical study in over 8,000 patients found that there was insufficient support for these risks and the black box was removed. It is hypothesized that some of the off-target effects of varenicline stem from off-target receptor binding. Nausea is associated with the 5-HT_3 receptor and there is a relationship involving the α-7 receptor, long-term memory and schizophrenia.

[13] https://xtalks.com/pfizers-chantix-compared-to-nicotine-patches-220/

Pricing

Pricing for Chantix in the United States is from $1,200 to $1,300 per course of treatment and it is covered by most insurance plans, Medicare and Medicaid.[14]

Zyban (bupropion hydrochloride)

Bupropion was first approved in 1985 for depression under the brand name Wellbutrin and was removed from the market the following year due to incidence of seizures. In 1997, the drug was approved as a smoking cessation aid under the name Zyban in the United States and in subsequent years, Europe as well. Generic versions of bupropion became available in 2006. The drug belongs to the aminoketone class, and is distinct from other antidepressant agents. It is a weak inhibitor of reuptake of dopamine, noradrenaline and serotonin in the central nervous system. It is also a non-competitive nicotine receptor antagonist and in combination with suppressing the reward transmitters is useful in reducing the cravings for cigarette smoking. Bupropion has been observed to be more effective than NRT when combined with behavioral support[15] but less effective than varenicline based on a review of clinical trials.[16]

Treatment with bupropion should be started prior to a selected quit date, giving time to achieve steady state blood levels of the drug before ceasing cigarette use. Initial administration begins with a daily dose of 150 mg for the first three days, then doubled to 300 mg afterwards. Treatment lasts for seven to twelve weeks and in some cases can extend longer if patient and physician agree.

Side Effects and Contraindications

Adverse events from bupropion treatment include agitation, dry mouth, insomnia, headache/migraine, nausea/ vomiting, constipation and tremor. Some patients have discontinued use of bupropion due to neuropsychiatric disturbances (3.0%), gastrointestinal disturbances, including nausea and vomiting (2.1%), neurological disturbances such as seizures, headaches and sleep disturbances (1.7%), and skin problems, primarily rashes (1.4%). In patients that are trying to quit smoking, hostility, agitation, depression and suicidal thought or actions have been observed. Zyban product labeling includes information regarding psychosis, paranoia, anxiety, and other potential neuropsychiatric reactions.

Pricing

Zyban/bupropion is generic and is available for about $50 for the recommended duration of treatment.

Behavioral Therapy

Many studies[17] have shown that the addition of behavioral therapy to a smoking cessation plan improves overall success. Smokers with a strong addiction and ingrained habits need to change addictive behaviors. Behavioral therapy can increase an individual's confidence about being successful and help them avoid smoking triggers and teach methods to cope with the desire to smoke. Behavioral therapy has been used in conjunction with a number of medications in drug trials in an effort to improve smoking cessation rates. The protocol that that has been acknowledged by the FDA and other authorities for use as part of a clinical trial provides up to twelve behavioral support sessions that occur during initial screening, randomization and each visit. Counselors at these sessions will encourage the patients to overcome challenges and discuss anticipated side effects during an estimated 10 minute session.

[14] https://www.npr.org/sections/health-shots/2016/01/05/462017590/medicaid-programs-fall-short-when-it-comes-to-helping-smokers-quit
[15] Roddy, Elin. Bupropion and other non-nicotine pharmacotherapies. BMJ. 2004 Feb 28; 328(7438): 509–511.
[16] Ping, W. et al. 'Effectiveness of smoking cessation therapies: a systematic review and meta-analysis.' BMC Public Health. 2006.
[17] Sykes, C.; Marks, D. Effectiveness of a cognitive behaviour therapy self-help programme for smokers in London, UK. Health Promotion International, Volume 16, Issue 3, 1 September 2001, Pages 255–260

Something New From Something Old

Cytisine

Cytisine is an alkaloid that is produced naturally in several plants including those in the *Laburnum* and *Cytisus* genera. The molecular structure of the compound is similar to nicotine and has similar pharmacological effects. Cytisine is derived from the seeds of the *Laburnum anagyroides* plant, also known as golden chain, which grows in mild and damp climates in central and southern Europe. The plant is a bush or tree and can reach heights of 23 feet. It produces black seeds, which are very poisonous to humans, goats and horses if ingested whole. From first planting, it takes four to five years for the plant to produce the seeds from which the cytisine is taken. Achieve's supplier Sopharma AD extracts cytisine from the plant in its production facility by processing the seeds.

The plant and its derivative have a long history associated with smoking. During World War II, the leaves of the plant were used by smokers as a tobacco substitute by Russian soldiers. In the 1960s, clinical trials took place in Central and Eastern Europe and former Soviet states and the product was first marketed in Bulgaria in 1964. In succeeding years it also became available in Poland, Russia and adjacent states as a cost effective clinical treatment for nicotine addiction.

In the fourth quarter on 2018, the United States Adopted Names Council designated cytisinicline as the generic name for cytisine. We use the terms relatively interchangeably, favoring cytisinicline when referring to Achieve's relationship to the drug.

Exhibit III – Laburnum Anagyroides[18]



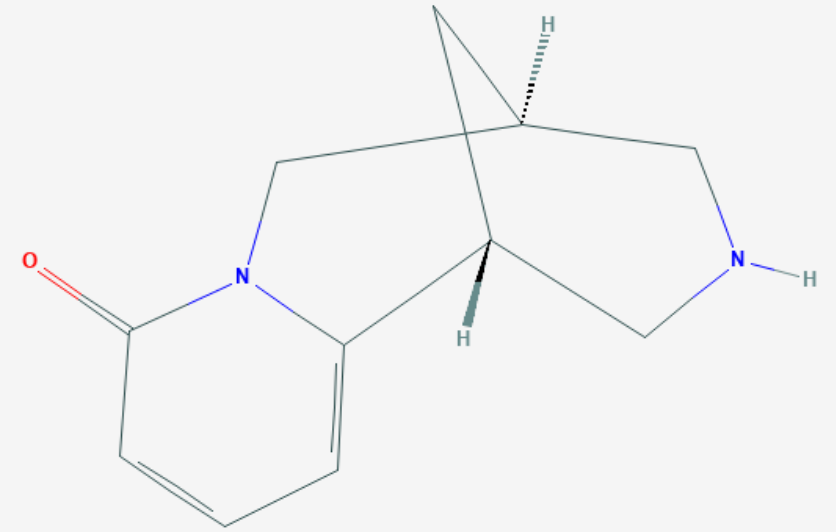
Mechanism of Action

Similar to nicotine and varenicline, cytisinicline binds to nicotinic acetylcholine receptors in the brain. Cytisinicline is a partial agonist for the $\alpha_4\beta_2$ nicotinic receptors which are central to the reward pathway for nicotine and result in addiction. The plant-based alkyloid stimulates the $\alpha_4\beta_2$ nAChR which results in excitation of the respiratory center, resulting in enhanced reflexes, simulation of adrenaline release by the medullar part of the suprarenal glands and a rise in blood pressure. For smokers, cytisinicline reduces the interaction between nicotine and the corresponding receptors in the gastrointestinal tract. The process decreases and interrupts the physical and psychological addiction to nicotine.

Cytisinicline has a chemical structure similar to nicotine and varenicline with a chemical formula of $C_{11}H_{14}N_2O$. It is a heterotricyclic compound with a ring of three elements. The following exhibit is an illustration of the chemical structure.

[18] Source: Wikipedia Commons. https://en.wikipedia.org/wiki/Laburnum_anagyroides

Exhibit IV – Chemical Structure of Cytisinicline



As derived from the *Laburnum anagyroides* plant, cytisinicline is near 100% the negative enantiomer or isomer of the cytisinicline molecule. While cytisinicline can be manufactured in the lab, the result consists of both the negative and positive enantiomer, and the process to isolate the desired cytisinicline structure is costly, difficult and incomplete. Research[19] has shown that the positive enantiomer of the molecule does not have a nicotinic profile and could possibly have off-target effects. The isomeric purity of naturally derived cytisinicline may contribute to the anticipated lack of off target effects that are present in competitor varenicline. Cytisinicline may provide more selective receptor targeting, including high affinity binding for the $\alpha_4\beta_2$ receptors and lower affinity for the α_7, 5-HT_3 and $\alpha_3\beta_4$ receptors which are thought to be associated with the vivid dreams and nausea observed with varenicline.

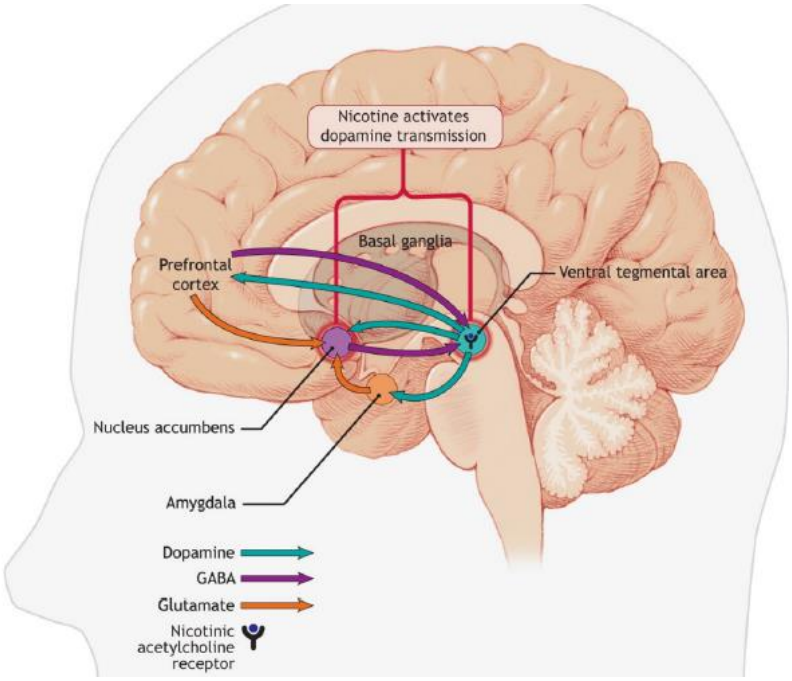
Exhibit V – Comparison of Receptor Binding

Site	Receptor	Cytisinicline	Varenicline
Brain	$\alpha_4\beta_2$	✓	✓
	α_7		✓
	5-HT_3		✓
Periphery	$\alpha_3\beta_4$		✓

Cytisinicline is both a partial agonist that fully occupies the agonist binding site while having low efficacy in activating the receptor. This has the benefit of partially stimulating dopamine release and reducing nicotine cravings and the severity of withdrawal symptoms. Cytisinicline also acts as a partial antagonist, which blocks the receptor without activating it and prevents nicotine from attaching. Failing to activate eliminates the rush that smokers get from the nicotine binding to the receptor limiting the consequences of nicotine exposure while taking cytisinicline.

[19] Gray, D., Gallagher, T. A flexible strategy for tri- and tetracyclic lupin alkaloids. synthesis of (+)-cytisine, (±)-anagyrine and (±)-thermopsine. Angew. Chem. Int. Ed., 45 (2006), pp. 2419-2423

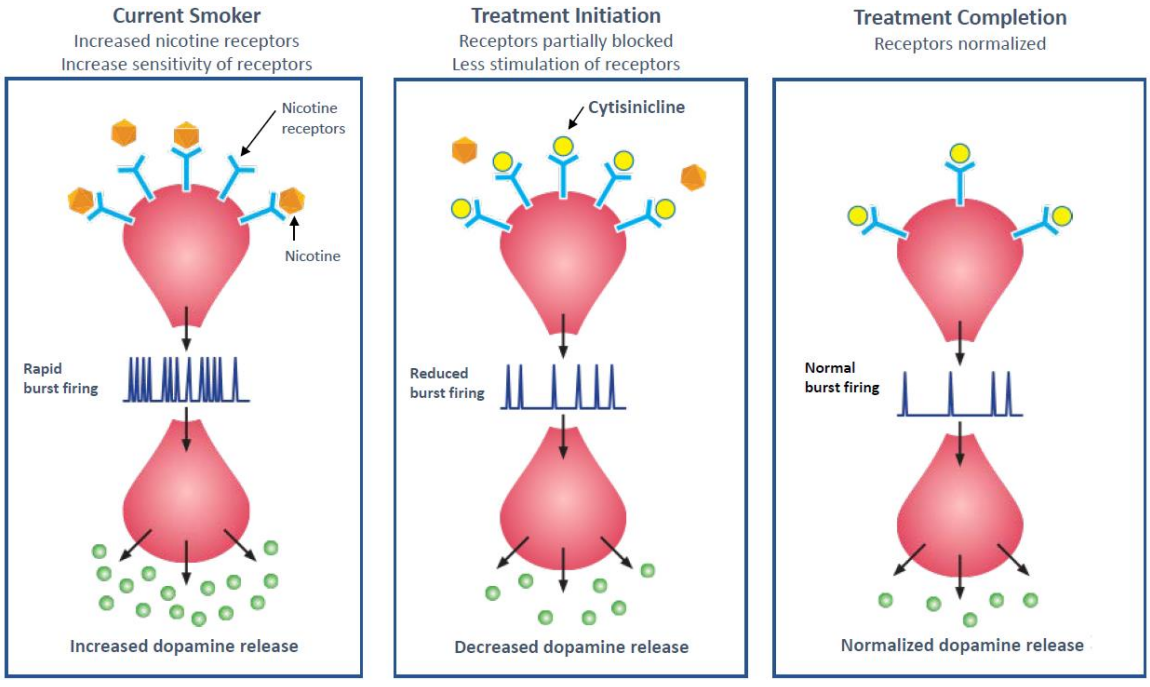
Exhibit VI – Cytisinicline Binding Sites in the Brain



Cytisinicline specifically targets the $\alpha_4\beta_2$ nicotinic receptors which prevents nicotine from binding, but still provides for some dopamine release to taper off the desired stimulation the smoker has come to expect. After a course of treatment with the drug, and a period of reduced dopamine release, the number of nicotinic receptors on neurons decreases to normalized levels and the patient's strong urge to smoke dissipates.

The following exhibit illustrates how the cytisinicline molecule attaches to $\alpha_4\beta_2$, preventing the attachment of nicotine. Over the recognized 25-day course of treatment, the number of receptors on the neurons normalizes both in terms of number and sensitivity. The patient also becomes accustomed to the lower level of dopamine release and the cravings for nicotine and to smoke dissipate.

Exhibit VII – Action of Cytisinicline During Treatment



Cytisinicline reduces the effects of nicotine on dopamine release and also tempers nicotine withdrawal symptoms that accompany nicotine cessation.

Adverse Events

The Cochrane Group conducted a literature review of studies performed for cytisinicline, and it found no severe adverse reactions at therapeutic doses. Discontinuation did occur in some investigations ranging from 6% to 15.5%. The adverse events observed were mild to moderate and transient in nature. Since the use of the drug is correlated with the reduction or elimination of smoking and the consumption of nicotine, some of the adverse events may be attributed to the absence of nicotine. Some of the highest incidence events included irritability (36%), dry mouth and throat (35%), appetite changes (47%), weight gain (21%), abdominal pain (0-20%), tachycardia (1-14%), nausea (1-11.5%), headache (1-17%), sleep disturbances (1-21%), mood changes (15%) and anxiety (11%). Other side effects occurred in 10% or less of the observed population.[20] Below we provide a summary of the incidence of the most commonly reported adverse effects. We note that these were not obtained from a head to head comparison, which does limit comparability to some extent. However, we also note the material difference in the incidence of these adverse events. There is currently a trial underway (see RAUORA) that directly compares cytisinicline and varenicline; however, results are not expected anytime soon.

Exhibit VIII – Adverse Event Profile Comparison

Adverse Event (95% CI)	Cytisinicline*	Varenicline**
Nausea/Vomiting	4.1% (3.0% – 5.4%)	27.8% (26.8% - 28.8%)
Sleep Disorder/Abnormal Dreams	2.5% (1.7% - 3.6%)	12.5% (11.8% - 13.3%)
Insomnia	0.2% (0.03% – 0.68%)	14.2% (15.6% - 14.9%)
Headache	1.4% (0.9% - 2.3%)	12.7% (12.0% - 13.5%)

Cytisinicline Clinical History

Cytisinicline was first tested[21] in humans in the 1960s in Bulgaria. Additional studies were performed in East and West Germany, Poland and Russia; however, few of the research papers were published in English and many of the studies did not meet the standards required for US or EU regulatory approval. After traversing the clinical trial process in East Germany, Poland, Bulgaria and a few other countries, the drug was subsequently marketed in former Soviet bloc nations to treat nicotine addiction. Since 2006, the compound has been tested in two completed Phase III clinical trials which enrolled over 2,000 patients.

TASC Trial

The Tabex Smoking Cessation (TASC)[22] trial was a 740-patient study designed with a double-blind, placebo-controlled structure. The trial was conducted in Poland, where Tabex (cytisinicline) was already approved. The first patient was enrolled in December 2007 and the drug was dosed for 25 days, but only limited counseling was provided to participants. Trial results showed that 8.4% of the cytisinicline group was abstinent for a sustained period after 12 months while 2.4% was abstinent in the placebo group. The study found cytisinicline was more effective than placebo for smoking cessation.

The trial measured its primary endpoint of smoking abstinence with an expired air Carbon Monoxide (CO) reading at the twelve month follow-up date of less than 10 ppm. This is in contrast to other studies which used the more subjective patient reporting of their smoking habits. Secondary endpoints include 1) abstinence rate two weeks after the quit date, 2) self-reported continuous abstinence during first four weeks of treatment, 3) severity of withdrawal symptoms, 4) minor and serious adverse events reported and 5) depression, mood and physical symptoms reported.

[20] Tutka, P. et al. Cytisine for the treatment of nicotine addiction: from a molecule to therapeutic efficacy. Pharmacological Reports. 2005, 58, 777-798.
[21] Stoyanov, S., Yanachkova, M. Tabex – Therapeutic Efficacy and Tolerance. The Neuropsychiatric Research Institute. 2nd Psychiarty Center, Savr. Med. XXIII, 1972, 6, 31 – 33.
[22] West, R., Zatonski W., Cedzynska M., et al. Placebo-controlled trial of cytisine for smoking cessation. N Engl J Med 2011;365:1193-1200

The medication regimen was for a duration of 25 days. For days one to three, six 1.5 mg tablets were taken every two hours. Days four to twelve, five 1.5 mg tablets were taken and days 13 to 16, four tablets, days 17 to 20, three and the final five days two tablets per day were consumed.

Following the 25 day course of treatment of either cytisinicline or placebo, 12-month abstinence was 8.4% in the cytisinicline group and 2.4% in the placebo group, a 6.0 percentage point difference.

Adverse events were higher in the cytisinicline arm with gastrointestinal events in 13.8% of the cytisinicline population compared with 8.1% in the placebo arm. Psychiatric events, including dizziness and somnolence, occurred in 4.6% of the active arm and 3.2% in the control arm. Other events including nervous system events and skin and tissue reactions were small and there were insignificant differences between the populations. There were seven serious events, four in the cytisinicline group and three in the placebo group and they included death due to lung cancer, cardiac arrest, stroke and COPD.

The study concluded that cytisinicline was effective for stopping smoking and observed that it could be even more effective if combined with behavioral support. The authors also noted that the treatment period was much shorter that therapy durations for alternative approaches such as NRT at eight weeks and varenicline at 12 weeks.

CASCAID New Zealand Study[23]

A Phase III, open label, noninferiority trial was conducted in New Zealand in 2014 with 1,310 adult smokers and a primary endpoint of continuous abstinence at one month. Enrollees were randomly and equally assigned into a cytisinicline arm for 25 days of therapy or a NRT arm for eight weeks. NRT therapy included nicotine patches, gum, lozenges, or both gum and lozenges. The trial showed favorable results for the cytisinicline arm with 40% of the group reporting abstinence from smoking while only 31% of enrollees in the NRT arm reported this status. The trial combined the assigned drug with behavioral support, which included three calls of 10 – 15 minutes each over the measurement period of eight weeks.

Adverse events were more frequent in the cytisinicline arm (31% of participants) compared to the NRT arm (20% of participants. However, most adverse events were mild or moderate. Serious adverse events were 7% for the cytisinicline arm and 6% in the NRT group. It is unclear how many of the adverse events were attributable to the drugs used in the study. A complete summary of the safety data is available here. Nausea, vomiting and sleep disorders were the most common events.

The investigators running the trial concluded that cytisinicline was superior to NRT therapy for dependent smokers that were motivated to quit. The drug appears to be effective as a smoking cessation aid in first line therapy for nicotine dependence.

RAUORA New Zealand Study

The Cytisine vs. Varenicline for Smoking Cessation (RAUORA)[24] Phase III trial is currently underway in New Zealand. It is a head to head comparison of cytisinicline and varenicline that is evaluating the safety, efficacy, and cost of cytisinicline and behavioral support compared to varenicline and behavioral support for smoking cessation. The trial is being conducted in the native Māori population.

The study, which began in late 2017, seeks enrollment of 2,140 individuals who are Māori or family of Māori. It consists of 12 weeks of treatment and subsequent monitoring for up to a year where participants will be randomized 1:1 between cytisinicline and varenicline. It will be designed as an open-label, randomized, non-inferiority trial. The primary endpoint will be smoking cessation six months after the quit date as measured by carbon monoxide expired breath meter. Secondary endpoints look at absence of smoking at other intervals and time to relapse, if it occurs.

There will be an update by the trial investigators on enrollment numbers in 2019, but there will be no interim readout. As of last October, 500 or about a quarter of targeted participants had been enrolled. This will be the first head to head trial comparing cytisinicline and varenicline and is expected to provide indications of these two smoking cessation therapies.

[23] Walker, N. et al. Cytisine versus Nicotine for Smoking Cessation. New England Journal of Medicine 2014; 371:2353-2362
[24] The title of the trial is the Māori word Rauora which means rescue. https://glosbe.com/mi/en/rauora

Achieve Sponsored Trials

In June 2017 Achieve filed its investigational new drug (IND) application with the FDA and in August began its first study regarding the bioavailability of cytisinicline under fed and fasted conditions in normal healthy volunteers. Results of the trial were provided in November 2017 and demonstrated no food effect with similar bioavailability in both groups.

In October 2017, Achieve began its pharmacokinetic (PK) and pharmacodynamics (PD) trial to measure the effects of a 1.5 mg and 3.0 mg dose of cytisinicline. The trial evaluated 26 healthy smokers, ages 18 to 65 and administered the 25-day standard course of treatment. Final results announced February 2019 indicated that 46% of the enrollees had biochemically verified smoking abstinence by day 26 and there was an 80% reduction in cigarettes smoked. Biochemically verified smoking cessation rates were 39% in the 1.5 mg arm and 54% of the 3.0 mg arm. Observed adverse events were mostly mild and headaches were the most common reported event.

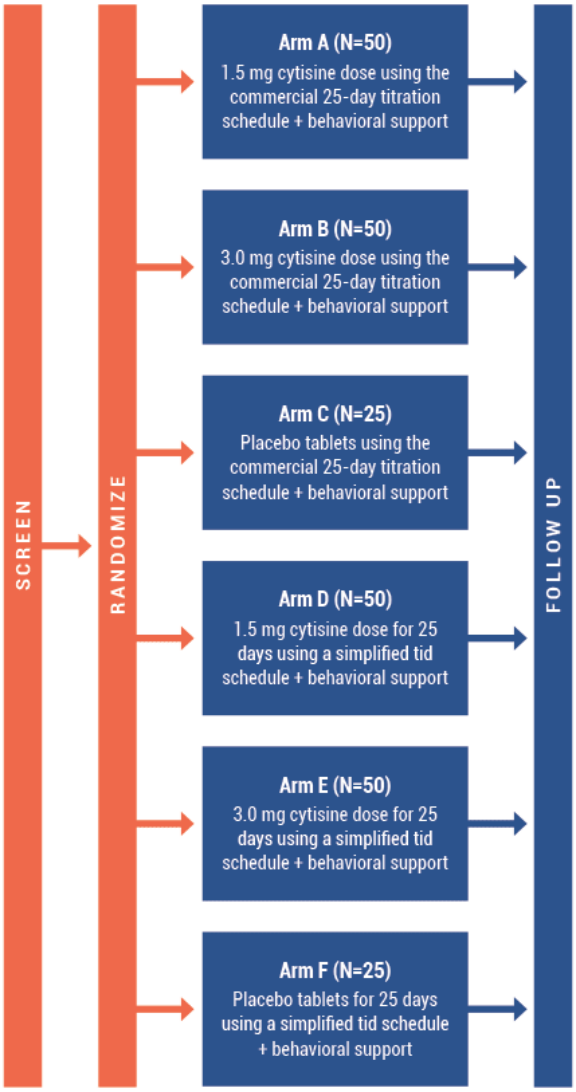
In December 2017, drug metabolism, drug-to-drug interaction and transporter studies were launched for cytisinicline, which were later included in the IND demonstrating the drug metabolism and providing evidence that cytisinicline may be administered with other medications without the need to modify the dose of the companion drug.

In May of 2018, the company held its end of Phase II meeting with the FDA where the agency provided guidance on Phase III trial design and the development path to NDA for cytisinicline.

ORCA Trial

The Ongoing Research of Cytisinicline for Addiction (ORCA)-1 trial was launched in October 2018 as a Phase IIb optimization study. It has enrolled 254 smokers to evaluate the 1.5 mg and 3.0 mg doses of cytisinicline over the 25 day administration period using either a declining titration schedule or three daily doses. Data from ORCA-1 will be used to finalize the design of the Phase III program. The Phase IIb is designed as a multicenter, double blind, placebo-controlled trial in adult smokers randomized in a 2:2:1 ratio at 1.5 mg, 3.0 mg and placebo. It will compare the use of 1.5 mg and 3.0 mg of cytisinicline and behavioral support against a placebo comparator and behavioral support in eight trial locations in the US. Subjects will also be stratified by weight class. The primary endpoint is the percentage reduction in cigarettes smoked during treatment. Secondary analyses will examine smoking cessation rates, safety and compliance. The Data Safety Monitoring Committee has reviewed trial data and concluded that there are no safety concerns and that the trial should proceed as planned. On March 20, 2019, the company announced that enrollment was complete, with all 254 patients participating. Results from the trial are expected in mid-2019.

Exhibit IX – ORCA-1 Study Design



Phase III Trials

Following the completion of the Phase IIb trial, Achieve will finalize the design of two Phase III trials in conjunction with the FDA's guidance. For the smoking cessation indication, the FDA requires two Phase III trials and for cytisinicline which will be structured similarly to the ORCA-1 trial and will additionally provide consideration for body mass index (BMI). The first trial is slated to begin before year end 2019 and will enroll 800 patients. It will be a two arm trial comparing cytisinicline with placebo and is anticipated to last approximately one year. The second Phase III trial is targeted to begin in the first half of 2020 and will enroll 1,500 patients in a three-arm trial examining 1.5 mg and 3.0 mg doses. The larger trial is expected to last approximately

18 months. Both of the studies will use behavioral support in each of the arms and have a primary endpoint of 4 week continuous abstinence rate post treatment. Abstinence will also include a measurement of exhaled carbon monoxide (CO) as biochemical verification of abstinence. Abstinence or smoking cessation will continue to be evaluated monthly for six months after initial randomization in order to provide a measure of long term, biochemically confirmed smoking cessation. Secondary endpoints will include intermediate quit rates, safety and compliance similar to what has been measured in other registrational trials. Final protocol will be confirmed following analysis of Phase IIb results and additional consultation with the FDA. If the initial targeted timelines for the trials are maintained, both trials should be complete near year end 2021 or early 2022.

Chemistry, Manufacturing and Control (CMC)

Achieve will source supply for cytisinicline from Sopharma's facility in Sofia, Bulgaria. Their new facility which was opened in November 2013 has a capacity of four billion tablets per year. It is EU-GMP compliant and has been inspected by a number of EU qualified persons (QP) as they perform contract manufacturing for product sold into the EU. As part of the submission of an NDA, the FDA will also inspect the facility. Achieve has already engaged two independent auditors to examine the facility with FDA requirements in mind. In conjunction with Sopharma, the company is working on a program to ensure the the specific requirements for the FDA that differ from EU requirements will be addressed by the time the NDA is filed.

Intellectual Property

Achieve holds several patents for cytisinicline in solid dosage form. The company is also developing several salts of cytisinicline to improve stability in lactose; however, it is unlikely that these will be utilized for the current development effort. Bridging studies would be required prior to approval to switch to a patent protected formulation. Cytisinicline is a natural substance and therefore cannot be patented in its base form as per US Supreme Court rulings. Even in the absence of any patent protection, cytisinicline would obtain five years of exclusivity as a new product[25] in the United States from the FDA. In Europe, when a company brings a new product to market that is not already approved, they are eligible for the "8+2+1" regime, which allows for eight years of data exclusivity, an additional two years of marketing exclusivity and a one year extension to marketing exclusivity if a new therapeutic indication is authorized[26] through the EU Data Exclusivity Directive.

Financial Position

As of September 30, 2018 Achieve Life Sciences held approximately $13.1 million in cash and cash equivalents and short-term investments on its balance sheet. In early October, 2018, the company raised approximately $5.0 million through registered direct offering. During 2018, the company has raised proceeds of approximately $19.8 million from sale of preferred stock, equity, warrants and proceeds from a purchase agreement with Lincoln Park Capital providing sufficient funds to reach into the third quarter of 2019. We anticipate expenditures of approximately $3.5 million per quarter, but also expect a high degree of volatility from period to period due to uneven trial costs and timing of trial-related R&D payments. For the trailing four quarters ending September 30, 2018, Achieve consumed approximately $9 million in cash from operations and capital investments. The company holds no debt on its balance sheet. We anticipate a capital raise in the first half of 2019 in order to fund the late 2019 launch of the Phase III cytisinicline smoking cessation study.

Management has identified that the two phase three trials will cost approximately $12 million for the 800 person trial and approximately $20 million for the 1,500 person trial. We also anticipate that there will be a baseline R&D spend of about $2 million per quarter. This suggests that Achieve will need to raise $50 million to fund the trials over the next two years. Additional amounts will be needed in 2021 to complete the trials and submit a new drug application to the FDA. The actual amount of capital raised will be dependent on market conditions and estimated dilution at the time of issuance.

Subsequent to the end of the quarter, Achieve completed a registered direct offering and sold 1.80 million shares of stock at $3.14 per share. Attached to each share was one half warrant with an exercise price of $3.14 per share with an expiration date in October 2023. Gross proceeds were $5.6 million and after deducting related expenses, net cash raised was $5.0 million.

[25] A sponsor may apply for NCE exclusivity for "a drug that contains no active moiety that has been approved by FDA in any other application submitted under section 505(b) of the Act." The active moiety of a drug is the molecule or ion responsible for the physiological or pharmacological action of the drug.

[26] The EU has adopted a harmonized approach to data and marketing exclusivity under Regulation (EC) No. 726/2004 and Directive 2001/83/EC. The exclusivity scheme applies to products that have been authorized in the EU by either the European Commission, through the centralized procedure, or the competent authorities of the Member States of the European Economic Area, or EEA, under the Decentralized or Mutual Recognition procedures.

Key Events

- Sopharma license agreement signed – 2009
- Sopharma supply agreement signed – 2010
- TASC study results published in NEJM – 2011
- CASCAID study results published in NEJM - 2014
- Achieve created and acquires all rights to cytisine excluding Sopharma territories – May 2015
- University of Bristol license agreement signed – July 2016
- Oncogenex & Achieve merger agreement date – January 5, 2017
- Investigational new drug (IND) application filed with FDA for cytisine – June 2017
- Merger completed with Oncogenex & listing on NASDAQ under ACHV – August 2017
- Food bioavailability study initiated – August 2017
- Pharmacokinetic study in smokers initiated – October 2017
- Food bioavailability results for fed and fasted – November 2017
- In vitro drug to drug interaction studies initiated – December 2017
- Submitted request to FDA for pre-Phase III meeting with FDA – December 2017
- Preliminary results from Phase I/II repeat dose pharmacokinetic/pharmacodynamic study – February 2018
- End of Phase II meeting – May 2018
- Completion of drug-drug interaction studies – June 2018
- Initiation of Phase IIb trial in US – October 2018
- $5.6 million capital raise – October 2018
- Last patient enrolled in Phase IIb – February 2019
- Repeat dose final study final results release – February 2019
- Last patient, last visit Phase IIb – 2Q:19
- Launch 800 person Phase III trial – 4Q:19
- Launch 1,500 person Phase III trial – first half 2020
- Complete 800 person Phase II trial 4Q:20
- Complete 1,500 person Phase III trial – year end 2021
- Submit NDA to FDA – 2022
- FDA response and launch of cytisinicline - 2023

RISKS

All investments contain an element of risk which reflects the uncertainty of the business and what it will ultimately achieve. Some investments exhibit higher predictability, with current cash flows and established sales. These enterprises will have a lower level of perceived risk while other companies that are betting on an emerging technology will have a much higher level.

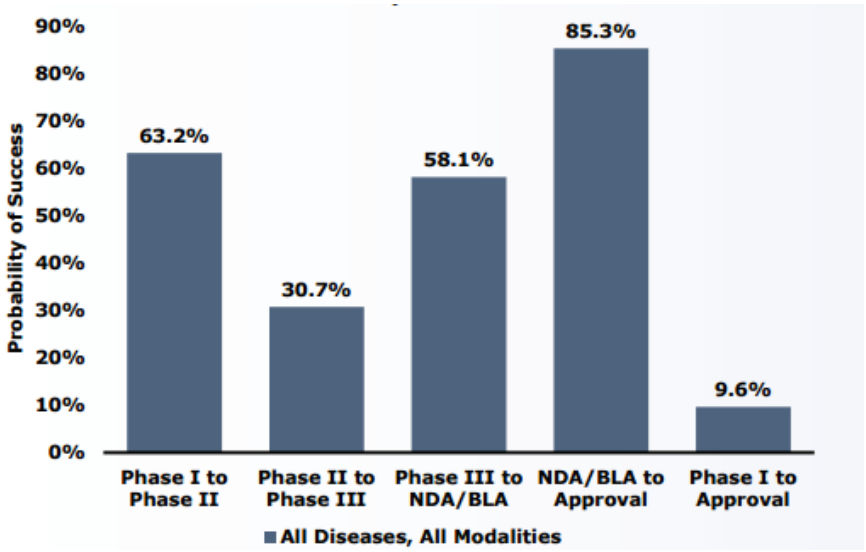
The biotechnology space includes companies at both ends of the spectrum, from mega-cap pharmaceutical powerhouses that have multiple products currently generating revenues, to small operations with a handful of employees conducting pre-clinical studies. Many of the risks faced by the large pharmaceutical companies and smaller biotechnology-focused firms are similar; however, there are some hazards that are particular to smaller companies that have not yet established themselves or their products.

For smaller early-stage companies, investing in drug development is an extended process. The timeframe between conducting pre-clinical research and eventually marketing a new chemical entity can take from 12 to 15 years or even longer given market conditions. And with, on average, only one in one thousand compounds eventually making it to the market, the risks are substantial.

Even if a company has a strong, experienced team that is developing a therapy with a high likelihood of success and a large addressable market, securing funding may pose a substantial risk. Access to financing comes and goes in cycles. During periods of improving confidence, capital may be easy to access; however, during a liquidity crisis or a period of heightened risk perception, even companies with bright prospects may be in trouble if they are dependent on the financial markets to fund their work. If capital is needed to sustain the company and it is not readily available, it may be forced to suspend operations, sell equity at a substantial discount to previous valuations and dilute earlier shareholders. A lack of funding may leave potentially promising therapies without a viable route to move forward or force a company to accept onerous terms.

All drugs must navigate the regulatory approval process in the US, EU and other countries before commercialization in those regions. This effort is a material uncertainty which may take years depending upon the needs and desires of the determining authority. Substantial expense is undertaken to bring a molecule or compound through clinical trials and address all of the regulatory agencies' concerns. Isolating companies that have a long history of research success in drug development, with opinion leaders and experts in the field are important fundamentals that can help mitigate this risk. Companies and management teams that have had previous success with the FDA or other regulatory agencies also are more attractive than those who may be new to the process. Some accelerated pathways toward approval have been put forth such as that outlined in the Orphan Drug Act, however, changes in sentiment or perceived safety for pharmaceuticals drugs could change the regulatory environment to demand a more thorough process and these pathways may be extended or additional requirements may be put in place.

Exhibit X – Success of Phase Trials and Regulatory Approval[27]



[27] Clinical Development Success Rates 2006-2015. David W. Thomas, Justin Burns, John Audette, Adam Carroll, Corey Dow-Hygelund, Michael Hay.

Currently, Achieve Life Sciences is navigating its lead compound through a Phase IIb trial and it anticipates two additional Phase III trials will be launched over the next 18 months. Historically, Phase III trials have a 50% chance of leading to ultimate FDA approval. Despite a long history of clinical trials for cytisine, Achieve will be pursuing two registrational trials as per FDA guidance to confirm the safety and efficacy of the product to generate data for an application that will follow the 505(b)(1) or traditional NDA pathway for a new chemical entity. We anticipate that the company will submit an NDA to the FDA following the successful conclusion of their second Phase III trial. Despite success in a Phase III trial, approval is not guaranteed and complete response letters (CRLs) and delays to originally anticipated timelines and target action dates are common. Achieve plans to pursue a dual commercialization approach for cytisinicline, partnering with an established pharmaceutical company for the primary care market, while developing their own salesforce for the specialty market of pulmonologists and smoking cessation centers. These are all high risk endeavors and many precedents of failures exist despite the best efforts of management teams and their employees.

In recent years, contract research organizations (CROs) have assumed a larger role in the development of drug candidates as the complexity and cost of trials has increased. Finding appropriate populations to participate in clinical trials has become increasingly difficult due to the shift to personalized medicine and orphan indications that address only a small population. This shift has increased the dependence on these specialized CROs for enrollee sourcing, project management and clinical monitoring services which add additional risks and dependence on third parties. Achieve is working with a smaller specialized CRO in its Phase IIb trial and using its key opinion leaders (KOLs) to guide the process in the smoking cessation space. The CRO does not have past experience running addiction management trials.

In addition to CROs, Achieve will rely on a third party manufacturer, Sopharma, for providing test and commercial quantities of cytisinicline. Risks of poor manufacturing processes, quality control issues and product delays may postpone ultimate production of the drug. Currently, the only cost-effective source of cytisinicline comes from the *Laburnum anagyroides* tree which is native to Eastern Europe. Achieve will be reliant on Sopharma to source the raw product from its tree farms, process the harvested seeds and manufacture clinical grade product according to current good manufacturing processes (cGMP). While Achieve may pursue an alternate supply of product, the product is now only manufactured by partner Sopharma, a Bulgarian-based pharmaceutical producer. The partner may lack the desire or skill to successfully obtain the approvals required to produce cGMP quality product and comply with FDA requirements. The partner may have other competing products under its control that receive greater company attention and resources.

Drug price inflation has gained increased attention over the last several years and has contributed materially to the increase in health care costs over the last decades. As new therapies have been approved, drug prices have set new records and increased at a substantial rate. The inflation rate for established drugs has also been very high. For example, in 2013 Chantix cost about $236 for a 30-day supply but increased to $485 in 2018, representing a 15% compound annual growth rate.[28] In a Forbes article, Novartis' leukemia drug Gleevec was highlighted. This drug cost $24,000 in 2001 when it was first approved; and 14 years later, in 2015, had risen to a cost of $90,000. This represents a 10% compound annual growth rate over that period. We also cite the broad response to Mylan's EpiPen price increases which have pressured the company to offer lower priced alternatives and encouraged competitors to accelerate the availability of generics. Achieve's strategy is to target pricing between the branded and generic prices for Chantix, anticipated to be between $500 and $1,500 per course of treatment following the availability of a generic competitor in 2020. We see a price between these amounts as easily absorbed with room for increases if cytisinicline exhibits improved success rates and reduced side effects. In addition, The Patient Protection and Affordable Care Act passed in 2010 requires health insurance plans provide coverage for two quit attempts annually, which includes both the prescription therapy and behavior support.

While we have discussed a broad variety of risks above, we believe that our forecast parameters, discount rates, success probabilities and valuation metrics address these eventualities and our target price reflects an assumption of these risks faced by all biotechnology companies.

[28] Prices for Smoking Cessation Drug Chantix Increase by 106% in Just Five Years. Tori Marsh, June 25, 2018.

PEERS AND COMPETITORS

There are many participants in the smoking cessation and NRT spaces including both companies that have products in development and products that are currently generating sales. We include a list of the most relevant peers and competitors below, ranked by market capitalization. With the exception of spray, inhaler and tablets, NRT is available over the counter and is manufactured and distributed by a broad number of health and wellness companies worldwide. NRT is the most popular approach to overcome nicotine addiction due to attractive price and ease of use. The two most popular prescription medications for smoking cessation are Chantix (varenicline) and bupropion. Pfizer's Chantix is generally recognized as the most effective available therapy. The drug surpassed $1 billion in sales in 2018, but will likely lose patent protection in 2020, spawning generic competitors after that date. Bupropion is generic and provided by a number of manufacturers with additional indications beyond smoking cessation on its label. Below we provide a summary of the key players in the market, including novel approaches such as PPAR gamma agonists for addiction and nicotine vaccines.

Exhibit XI – Smoking Cessation Peers and Competitors[29]

Ticker	Company	Price	MktCap (MM)	EV (MM)	Therapeutic Area
PFE	Pfizer	$43.36	$250,640	$275,470	Chantix/varenicline
GSK	GlaxoSmithKline	$40.39	$96,510	$99,420	Zyban/bupropion
PRGO	Perrigo	$50.13	$6,811	$9,490	NRT lozenge & gum
RDY	Dr. Reddy's Labs	$38.42	$6,403	$6,160	Habitrol patch
CIPLA.BO	Cipla Limited	₹ 551.65	₹ 445,230	₹ 465,370	NRT Gum & Patches
OMER	Omeros	$15.17	$743	$744	PPAR gamma agonist
XXII	22nd Century Group	$2.33	$290	$228	X-22: tobacco-based botanical medical product for use as an aid to smoking cessation
AXSM	Axsome	$7.94	$237	$229	AXS-05: bupropion/dextromethorphan
SELB	Selecta Biosciences	$2.13	$90	$19	SELA-070: Nicotine Vaccine for Smoking Cessation & Relapse Prevention
RSCI	Redwood Scientific Technologies	$0.02	$4	$3	Strip delivery technology (buccal & sublingual)
ARDM	Aradigm	$0.12	$2	N/A	ARD-1600: novel Inhaled Nicotine Therapy
pvt	Embera Neurotherapeutics				Addiction control for tobacco, cocaine, meth, eating, gambling and PTSD
pvt	Quit4Good				medicated oral strip designed to suppress the nicotine cravings and withdrawal symptoms
pvt	Chrono Therapeutics				CTI-100: Transdermal nicotine delivery systems
pvt	NAL Pharmaceuticals				Patch, lozenge, gum, film using captive delivery system
ACHV	Achieve Life Sciences	$2.45	$16	$3	Cytisinicline

[29] Price and market capitalization data is as of March 1, 2019

MANAGEMENT PROFILES

Richard Stewart, Chairman and Chief Executive Officer

Mr. Stewart has served as Achieve's Chairman and as a director since Achieve was founded in May 2015. He is also a founder and a director of Ricanto Limited, a pharmaceutical asset optimization company, since 2009. Mr. Stewart has been Chairman and Chief Executive Officer of Renown Pharma Limited, a central nervous system company focused on Parkinson's disease, since 2016.

Prior to Achieve, Mr. Stewart was Chief Executive Officer of Brabant Pharma Limited, a single purpose central nervous system company, from 2013 to 2014 prior to Brabant Pharma's acquisition by Zogenix Inc. Mr. Stewart was Chairman and Chief Executive Officer of Huxley Pharmaceuticals, Inc., a single purpose central nervous system company, during 2009, prior to Huxley Pharmaceuticals, Inc.'s acquisition by BioMarin Pharmaceutical Inc.

He was a co-founder and Chief Executive Officer of Amarin Corporation plc, a central nervous system company focused on Parkinson's disease and Huntington's disease, from 2000 to 2007. Mr. Stewart was a co-founder and Chief Financial Officer, and later Chief Business Officer, of SkyePharma plc, a drug delivery company specializing in controlled release formulations, and held positions at the company from 1995 to 1998. Mr. Stewart holds a Bachelor of Science degree in Business Administration from the University of Bath.

John Bencich, Executive VP, Chief Financial and Operating Officer

Mr. John Bencich is an experienced financial executive who has spent nearly 18 years guiding financial strategy in the life sciences and technology industries. Prior to joining Achieve Life Sciences in 2017, John served as CFO of OncoGenex Pharmaceuticals, a publicly traded biotechnology company. Before joining OncoGenex in 2014, John served as CFO of Integrated Diagnostics overseeing finance, corporate development, accounting and human resource functions. Prior to joining Integrated Diagnostics in 2012, John was CFO of Allozyne, a private, VC-backed company where he led the company's finance, accounting and information technology groups. Earlier he served as the CFO and Treasurer of Trubion Pharmaceuticals, a publicly traded biotechnology company where he helped complete the successful sale of the company to Emergent BioSolutions. Other roles include Director of Finance for Onyx Software Corporation, a publicly traded software company. John started his career at Ernst & Young LLP. He graduated from the University of San Diego with a BA in Accounting, earned his MBA from Seattle University and is a Certified Public Accountant.

Dr. Anthony Clarke, President & Chief Scientific Officer

Dr. Clarke has served as Achieve's Chief Scientific Officer and as a member of Achieve's board of directors since 2015. Dr. Clarke is a founder of Ricanto Limited and a director of the organization since 2009. From 2016 to the present, Dr. Clarke has been Chief Scientific Officer of Renown Pharma Limited. Dr. Clarke was Chief Scientific Officer of Huxley Pharmaceuticals, Inc. during 2009, prior to Huxley's acquisition by BioMarin Pharmaceutical Inc. Prior to Achieve, Dr. Clarke served as Chief Scientific Officer of Brabant Pharma Limited from 2013 to 2014 prior to Brabant Pharma's acquisition by Zogenix Inc. Dr. Clarke served as Company Secretary of Alexza UK Ltd. and as Vice President International Development Operations of Alexza Pharmaceuticals Inc., a pharmaceutical development company, holding both positions from 2008 to 2009. Dr. Clarke served as the Vice President, Clinical Research and Regulatory Affairs at Amarin Corporation from 2005 to 2008. In addition, Dr. Clarke was Senior Director, Clinical and Regulatory Affairs, of Cephalon Europe and as Senior Director, Worldwide Pain Management, of Cephalon, Inc. from 2000 to 2004. Dr. Clarke held a number of management roles in other pharmaceutical companies prior to 2000 as well as academic posts and honorary academic posts. Dr. Clarke holds a Bachelor's degree in Pharmacology from the University of Sunderland and a Ph.D. in psychopharmacology from the University of London. He was a Fellow of the Royal Statistical Society (UK) and is a current Fellow of the Royal Society of Medicine (UK).

Cindy Jacobs, Ph.D., M.D., Executive VP and Chief Medical Officer

Dr. Jacobs is an experienced executive in drug development with expertise in several indications and over 30 years' experience in the Biotechnology and Pharmaceutical industry. Dr. Jacobs has achieved regulatory success in several product approvals. Prior to joining Achieve Life Sciences in 2017, Dr. Jacobs served as OncoGenex's Executive Vice President and Chief Medical Officer since August 2008, and had been Executive Vice President and Chief Medical Officer of OncoGenex Technologies Inc. from September 2005 to August 2008. From 1999 to July 2005, Dr. Jacobs served as Chief Medical Officer and Senior Vice President, Clinical Development of Corixa Corporation. Prior to 1999, Dr. Jacobs held Vice President, Clinical Research positions at two other biopharmaceutical companies. Dr. Jacobs received her Bachelor's degree in Microbiology from Montana State University, her Master's degree and Ph.D. degree in Veterinary Pathology/Microbiology from Washington State University and an M.D. degree from the University of Washington Medical School. She has in-depth biotechnology experience in preclinical development, pharmacokinetic/drug metabolism studies, toxicology studies, clinical operations, Phase 1-4 trials in a variety of therapeutic areas, regulatory affairs, biostatistics, data management, medical information and quality assurance. Based on her preclinical work at Immunex Corporation, she is one of 2 inventors on the patent for Enbrel.

Jaime Xinos, Executive VP Commercial

Ms. Xinos has nearly 20 years of commercial experience in the biotechnology and pharmaceutical industries. She is an inspirational thought leader highly skilled in translating science into business as well as developing commercial strategies for specialty products across all stages of the product development continuum. Ms. Xinos currently serves as the Executive Vice President of Commercial at Achieve Life Sciences, which she joined in 2017. Prior to her current role, Ms. Xinos was Vice President, Marketing and Corporate Communications at OncoGenex Pharmaceuticals, an oncology biopharmaceutical company she initially joined as Senior Director, Global Oncology Commercial Development in 2010. Prior to OncoGenex, Ms. Xinos held various oncology commercial positions. She worked in marketing, commercial development and sales roles at Pfizer, Novartis and Abbott Laboratories. Ms. Xinos holds a degree in Communications from the University of Illinois and is completing her Master of Business Administration at the same institution.

Financial Results

Achieve Life sciences filed its third quarter 10-Q for the period ending September 30, 2018 on November 7, 2018 in conjunction with the accompanying press release and investor conference call. No revenues were reported for the development stage company as management efforts were focused on the initiation of the Phase IIb "ORCA-1" optimization trial. A key accomplishment in the period was the United States Adopted Name Council's (USAN) declaration of the generic name for cytisine as cytisinicline. Results from the fed and fasted study were also provided in the quarter, demonstrating no food effects.

Net loss for 3Q:18 was ($3.2) million or ($0.71) per share. This was comprised of operational costs of $3.3 million, offset by a small contribution from interest income. Total research and development expense of $1.5 million rose substantially from the $0.8 million in the prior year period due to expenses related to the repeat dose pharmacokinetics trial and a food effect study using a new formulation. Increased employee and facilities expenses were also recognized related to an increase in development activity.

General and administrative expenses were $1.8 million in the third quarter, rising from $1.6 million in 3Q:17. The 13% increase came from increases in employee headcount, consulting fees, legal fees and professional fees as a result of the closing of the merger and integration of OncoGenex.

Cash burn was ($3.0) million in 3Q:18, down from ($5.5) million in 3Q:17 due to merger related cash flows. Cash and equivalents and short-term investments as of September 30, 2018 were $13.1 million, an increase from year end 2016 levels of $5.3 million. The increase was attributable to share, warrant and purchase agreement issuances totaling $14.7 million offset by cash burn of ($7.1) million in the first nine months of the year.

Following the end of the quarter in October 2018, Achieve completed a direct offering of 1.80 million shares at $3.14 per share raising $5.6 million gross and $5.0 million net. One half warrant was attached to each share with a five year life and a $3.14 exercise price. Management noted that cash and equivalents at the beginning the fourth quarter stood at $18.2 million.

VALUATION

Cytisine has been used in Eastern Europe for many years with great success; however, the lack of clinical trials run at standards required by the FDA and EMA have prevented the product from being commercialized more widely. Achieve has recognized the potential of cytisine and has embarked on a mission to develop cytisinicline for approval in the United States. While broader approvals may be sought, the company's primary goal is to commercialize the drug in the US and our model will reflect this goal. We note that the vast majority of current smoking cessation revenues are generated in the US, despite 90% of total smokers residing outside the country. Achieve will pursue a dual development approach in the US and expects to partner with a large pharmaceutical company with an in-place primary care and internal medicine focus. Depending on the capabilities of the partner company, Achieve may also develop a specialty sales approach with its own team that will focus on pulmonologists, oncologists and smoking cessation centers.

Our forecasts call for first sales to occur in 2023, following FDA approval. With approximately 15% of the 2023 US population smoking and half of this number seeking a solution, we see an addressable market of 25 million. We estimate that Achieve's partner will be able to penetrate the market by 150 basis points in primary care for the first year of sales. This will rise modestly over the next six years to a peak penetration rate of 320 basis points. Generic competition is anticipated after this point; however, due to our conservative pricing estimates for cytisinicline, only modest market share is expected to be lost in the year when a generic option becomes available. Market share is expected to be flat in 2031 at 200 basis points (2%) of the addressable market. While it is difficult to estimate the negotiating position of Achieve following approval as this will depend on many factors including the strength of the data and the number of competitors vying for the partnership, we propose a 30% royalty on sales to be paid to Achieve.

We see Achieve building its own internal specialty sales force for commercialization outside of the primary care market. 20 to 30 representatives should be sufficient to start this endeavor, rising to 85 over the next five years and declining after this point as sales fall in sympathy with generic competition. Penetration into the addressable market of 50 million is expected to follow a similar path as the primary care market. First year penetration is expected to be 130 basis points increasing to 310 basis points (3.1%) of the addressable market after six years. Levels are expected to fall from here and level out after generic competition is fully recognized.

Cytisinicline pricing is forecast to be approximately $700 for a course of treatment in 2023. This is forecast to fall between a generic price for varenicline of about $500 and a branded price of greater than $1,500. This price point will also allow cytisinicline to avoid the hurdles imposed by payors where they enforce step edits and encourage penetration at ~$700. Modest annual price inflation of 2.5% is expected.

Based on the variables discussed above, we forecast revenues of about $300 million in the first year of sales, rising to a peak of almost $900 million in 2029. Following a step down to $500 to $600 million over the next few years, as a result of generic competition, sales should advance to the $700 million range and higher on market size increases and price inflation.

Cost of goods sold is very attractive for cytisinicline. While exact amounts that Achieve will pay to Sopharma for product and royalty are not publicly available, we forecast a mid-single digit royalty on net sales and cost of goods under $10 per treatment cost for packaged product, yielding a 93% gross margin. R&D is forecast to fall to zero following commercialization and G&A should be around $24 million growing at normal inflationary rates. Sales force expenses will start at about $4 million in annual cost with a forecasted 23 sales reps the first year, growing to $17 million with 85 sales reps in 2028. Taxes are expected to accrue at a 30% rate.[30]

We employ a DCF model to generate our valuation and use a 15% discount rate and to these assumptions we apply a 15% probability[31] of ultimate commercialization of cytisinicline in the United States during the Phase IIb study. We include additional shares in our calculation to reflect the additional anticipated capital required to take the candidate to commercialization. Our estimates yield a target price of $6.00 per share.

[30] We use a consistent 30% tax rate for our US-based companies which is a combination of federal and state rates. This reflects the 21% rate from the 2017 corporate tax reduction, an average 5% state rate and an additional amount to reflect our assumption that state rates will increase to compensate for less federal funding and the adjusted probability that federal rates will increase in the future.

[31] Clinical Development Success Rates 2006-2015. David W. Thomas, Justin Burns, John Audette, Adam Carroll, Corey Dow-Hygelund, Michael Hay.

CONCLUSION

Achieve Life Sciences obtained the rights to develop cytisinicline in the United States and the majority of the rest of world from Sopharma to address a poorly met need for smoking cessation. Despite having been used for many years in Eastern Europe in millions of patients, cytisinicline is considered a new chemical entity in the United States. While a natural substance cannot be patented, the molecule can secure five years of exclusivity in the US if granted FDA approval and patents on new formulations of the drug could provide an extension of this exclusivity period. We see the long history and well-understood safety profile of the drug as strong positives in support of successful Phase III trials. Based on our timing forecasts, Phase III trials can be completed by late 2021 and FDA approval can arrive in time for commercialization in 2023.

While there are a number of solutions for smoking cessation available, the success rate is low and no new therapies have been approved in over a decade. Of this group, varenicline (Pfizer's Chantix) is recognized has having the best success rates; however, high levels of adverse events are seen as one of the main obstacles to greater efficacy. Cytisinicline, with its anticipated greater specificity for the $\alpha_4\beta_2$ nAChR receptor and fewer off target effects, may show an improved side effect profile resulting in greater compliance and higher success than products that are now available. While it is too early to know what the safety and efficacy profile will be in a trial aligned with FDA protocols, early results are promising.

Key reasons to own:

- **Proven asset with use in over 20 million smokers**
- **Preliminary data shows improved efficacy and favorable side effect profile vs. current products**
- **Shorter therapy duration vs. other NRT or Chantix**
- **Dual acting MoA reduces cravings, withdrawal symptoms & prevents rush from smoking**
- **Previous Phase III studies completed in over 2,000 subjects demonstrate safety and efficiacy**
- **Pursuing smoking population of ~40 million in US and over one billion worldwide**
- **Smoking cessation medication market value of $4.6 billion in 2018**
- **Company maintains sufficient cash to complete currently active trials**

In summary, we believe that the long historical use of cytisine, generically known as cytisinicline, provides confidence that the upcoming Phase III trials will be successful and will provide the necessary data to obtain FDA approval, presenting a relatively low risk pursuit for a new chemical entity. If Phase III trials are able to show materially improved success over what varenicline has achieved, we anticipate even higher sales than what we forecast in our model. Based on our conservative estimates, shares of ACHV are undervalued relative to their potential and we initiate with a target price of $6.00.

PROJECTED FINANCIALS

Achieve Life Sciences, Inc. - Income Statement

Achieve Life Sciences, Inc.	2017 A	Q1 A	Q2 A	Q3 A	Q4 E	2018 E	2019 E	2020 E	2021 E
Total Revenues ($MM)	**$0.0**	**$0.0**	**$0.0**	**$0.0**	**$0.0**	**$0.0**	**$0.0**	**$0.0**	**$0.0**
	-					-	-	-	-
R&D	$3.1	$1.2	$1.0	$1.5	$1.6	$5.4	$8.0	$26.0	$21.0
G&A	$3.5	$1.8	$1.8	$1.8	$1.8	$7.1	$7.2	$7.6	$8.0
Operating Income	($6.6)	($3.0)	($2.8)	($3.3)	($3.4)	($12.5)	($15.2)	($33.6)	($29.0)
Interest Income	$0.0	$0.0	$0.0	$0.1	$0.1	$0.1	$0.3	$0.0	$0.0
Total Other Income	($7.0)	($0.0)	($0.0)	($0.0)	$0.0	($0.0)	$0.0	$0.0	$0.0
Pre-Tax Income	($13.6)	($3.0)	($2.8)	($3.2)	($3.4)	($12.4)	($14.9)	($33.6)	($29.0)
Taxes & Other	$3.1	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
Tax Rate	*$0.0*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*$0.0*
Net Income	($10.6)	($3.0)	($2.8)	($3.2)	($3.4)	($12.4)	($14.9)	($33.6)	($29.0)
Reported EPS	**($22.07)**	**($2.43)**	**($1.82)**	**($0.71)**	**($0.50)**	**($3.54)**	**($1.01)**	**($1.16)**	**($0.81)**
YOY Growth									
Shares Outstanding	0.5	1.2	1.5	4.5	6.7	3.5	14.8	29.0	36.0

Source: Company Filing // Zacks Investment Research, Inc. Estimates

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HISTORICAL STOCK PRICE

Achieve Life Sciences, Inc. – Stock Price Chart[32]



[32] Source: Price chart courtesy of barchart.com

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