UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 8-K

CURRENT REPORT
Pursuant to Section 13 or 15(d)
of the Securities Exchange Act of 1934
Date of Report (Date of earliest event reported): May 23, 2023

ACHIEVE LIFE SCIENCES, INC.
(Exact name of Registrant as Specified in Its Charter)

Delaware	**033-80623**	**95-4343413**
(State or Other Jurisdiction of Incorporation)	**(Commission File Number)**	**(IRS Employer Identification No.)**
22722 29th Drive SE, Suite 100 Bothell, WA		**98021**
1040 West Georgia, Suite 1030 Vancouver, BC, Canada		**V6E 4H1**
(Address of Principal Executive Offices)		**(Zip Code)**

Registrant's Telephone Number, Including Area Code: (604) 210-2217

N/A
(Former Name or Former Address, if Changed Since Last Report)

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions (see General Instruction A.2. below):

☐ Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)

☐ Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)

☐ Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))

☐ Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	**Trading Symbol**	**Name of exchange on which registered**
Common Stock, par value $0.001 per share	ACHV	The NASDAQ Capital Market

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act of 1933 (§230.405 of this chapter) or Rule 12b-2 of the Securities Exchange Act of 1934 (§240.12b-2 of this chapter).

Emerging growth company ☐

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

Item 7.01 Regulation FD Disclosure.

On May 23, 2023, Achieve Life Sciences, Inc. (the "Company") issued a press release announcing topline data from its Phase 3 ORCA-3 trial of cytisinicline for smoking cessation and nicotine dependence. Additionally, the Company held a conference call and webcast with a presentation of the Phase 3 ORCA-3 topline data.

A copy of the press release is attached as Exhibit 99.1 to this Current Report on Form 8-K. A copy of the presentation is attached as Exhibit 99.2 to this Current Report on Form 8-K.

The information furnished in this Item 7.01, including Exhibits 99.1 and 99.2, shall not be deemed "filed" for purposes of Section 18 of the Securities Exchange Act of 1934, as amended (the "Exchange Act"), or otherwise subject to the liabilities of that section, nor shall it be deemed incorporated by reference into any other filing under the Exchange Act or the Securities Act of 1933, as amended, except as expressly set forth by specific reference in such a filing.

Item 8.01 Other Events.

On May 23, 2023, the Company announced topline data from its ORCA-3 trial of cytisinicline for smoking cessation and nicotine dependence. Topline results are summarized as follows:

Both the 6- and 12-week cytisinicline treatment durations demonstrated statistically significant smoking cessation, or quit rates, on both the primary and secondary efficacy analyses compared to placebo.

12-Week Cytisinicline Efficacy Results

•Primary Endpoint: Subjects who received 12 weeks of cytisinicline treatment had 4.4 times higher odds, or likelihood, to have quit smoking during the last 4 weeks of treatment compared to subjects who received placebo ($p<0.0001$). The smoking cessation rate during weeks 9 through 12 was 30.3% for cytisinicline compared to 9.4% for placebo.

•Secondary Endpoint: The continuous smoking cessation rate from week 9 to week 24 was 20.5% for the 12-week cytisinicline arm compared to 4.2% for placebo, with an odds ratio of 5.79 ($p<0.0001$).

6-Week Cytisinicline Efficacy Results

•Primary Endpoint: Subjects who received 6 weeks of cytisinicline treatment had 2.85 times higher odds, or likelihood, to have quit smoking during the last 4 weeks of treatment compared to subjects who received placebo ($p=0.0008$). The smoking cessation rate during weeks 3 through 6 was 14.8% for cytisinicline compared to 6% for placebo.

•Secondary Endpoint: The continuous smoking cessation rate from week 3 to week 24 was 6.8% for the 6-week cytisinicline arm compared to 1.1% for placebo, with an odds ratio of 6.25 ($p=.0006$).

Subjects had an average age of 53 years, smoked a median of 20 cigarettes per day at baseline, and had a median smoking history of 36 years with 4 prior quit attempts.

Similar to findings from the Company's Phase 3 ORCA-2 study, cytisinicline was well-tolerated with no treatment-related serious adverse events reported. The most commonly reported (>5% overall) adverse events for placebo, 6-week cytisinicline, and 12-week cytisinicline were:

•Insomnia: (7.6%, 11.0%, 11.9%)

•Abnormal dreams: (5.7%, 9.1%, 7.7%)

•Nausea (7.3%, 9.5%, 6.9%)

•Headache (6.1%, 7.6%, 8.5%)

This current report contains forward-looking statements within the meaning of the "safe harbor" provisions of the Private Securities Litigation Reform Act of 1995, including, but not limited to, statements regarding the timing and nature of cytisinicline clinical development, data results and commercialization activities, the potential market size for cytisinicline, the potential benefits, safety and tolerability of cytisinicline, the ability to discover and develop new uses for cytisinicline, including but not limited to as an e-cigarette cessation product, and the development and effectiveness of new treatments. All statements other than statements of historical fact are statements that could be deemed forward-looking statements. The Company may not actually achieve its plans or product development goals in a timely manner, if at all, or otherwise carry out its intentions or meet its expectations or projections disclosed in these forward-looking statements. These statements are based on management's current expectations and beliefs and are subject to a number of risks, uncertainties and assumptions that could cause actual results to differ materially from those described in the forward-looking statements, including, among others, the risk that cytisinicline may not demonstrate the hypothesized or expected benefits; the risk that the Company may not be able to obtain additional financing to fund the development of cytisinicline; the risk that cytisinicline will not receive regulatory approval or be successfully commercialized; the risk that new developments in the smoking cessation landscape require changes in business strategy or clinical development plans; the risk that the Company's intellectual property may not be adequately protected; general business and economic conditions; risks related to the impact on our business of macroeconomic conditions, including inflation, rising interest rates, instability in the global banking sector, and public health crises, such as the COVID-19 pandemic and the other factors described in the risk factors set forth in the Company's filings with the Securities and Exchange Commission from time to time, including the Company's Annual Reports on Form 10-K and Quarterly Reports on Form 10-Q. The Company undertakes no obligation to update the forward-looking statements contained herein or to reflect events or circumstances occurring after the date hereof, other than as may be required by applicable.

Item 9.01. Financial Statements and Exhibits.

(d) Exhibits

The following exhibit is filed herewith:

Exhibit No.	Description
99.1	Press release by Achieve Life Sciences, Inc.
99.2	Phase 3 ORCA-3 Topline Data Presentation
104	Cover Page Interactive Data File (embedded within the Inline XBRL document)

SIGNATURES

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has caused this report to be signed on its behalf by the undersigned, thereunto duly authorized.

ACHIEVE LIFE SCIENCES, INC.

Date: May 23, 2023

/s/ John Bencich
John Bencich
Chief Executive Officer (Principal Executive and Financial Officer)

EXHIBIT 99.1

Achieve Life Sciences Reports Statistically Significant Smoking Cessation Benefit for Cytisinicline in Second, Confirmatory Phase 3 Clinical Trial

ORCA-3 demonstrated statistically significant topline results in primary and secondary smoking cessation endpoints for both 6- and 12-week cytisinicline treatment durations compared to placebo

Cytisinicline demonstrated 6x increase in odds of continuous smoking abstinence at 6 months

Cytisinicline treatment well tolerated with low rates of adverse events reported

Management to host conference call today, May 23 at 8:30AM EDT

SEATTLE and VANCOUVER, British Columbia, May 23, 2023 (GLOBE NEWSWIRE) – Achieve Life Sciences, Inc. (NASDAQ: ACHV), a late-stage pharmaceutical company committed to the global development and commercialization of cytisinicline for smoking cessation and nicotine dependence, today announced positive topline results from the Phase 3 ORCA-3 trial of cytisinicline. Consistent with the previously reported Phase 3 ORCA-2 study, ORCA-3 showed a statistically significant benefit in helping people to quit smoking compared to placebo, with low rates of adverse events.

ORCA-3 was designed to evaluate the efficacy and safety of 3mg cytisinicline dosed 3 times daily for a period of 6 weeks or 12 weeks compared to placebo. ORCA-3 randomized 792 adult smokers at 20 clinical trial sites in the United States. All participants received standard behavioral support for the duration of the trial. The primary endpoint for ORCA-3 was biochemically verified smoking cessation measured during the last 4 weeks of treatment. Subjects were monitored for smoking cessation for 24 weeks post randomization.

Both the 6- and 12-week cytisinicline treatment durations demonstrated statistically significant smoking cessation on both the primary and secondary efficacy analyses compared to placebo.

12-Week Cytisinicline Efficacy Results

- Primary Endpoint: Subjects who received 12 weeks of cytisinicline treatment had 4.4 times higher odds, or likelihood, to have quit smoking during the last 4 weeks of treatment compared to subjects who received placebo ($p<0.0001$). The smoking cessation rate during weeks 9 through 12 was 30.3% for cytisinicline compared to 9.4% for placebo.
- Secondary Endpoint: The continuous smoking cessation rate from week 9 to week 24 was 20.5% for the 12-week cytisinicline arm compared to 4.2% for placebo, with an odds ratio of 5.79 ($p<0.0001$).

6-Week Cytisinicline Efficacy Results

- Primary Endpoint: Subjects who received 6 weeks of cytisinicline treatment had 2.85 times higher odds, or likelihood, to have quit smoking during the last 4 weeks of treatment compared to subjects who received placebo ($p=0.0008$). The smoking cessation rate during weeks 3 through 6 was 14.8% for cytisinicline compared to 6% for placebo.

•Secondary Endpoint: The continuous smoking cessation rate from week 3 to week 24 was 6.8% for the 6-week cytisinicline arm compared to 1.1% for placebo, with an odds ratio of 6.25 (p=0.0006).

ORCA-3 subjects had an average age of 53 years, smoked a median of 20 cigarettes per day at baseline, and had a median smoking history of 36 years with 4 prior quit attempts.
Similar to ORCA-2 findings, cytisinicline was well-tolerated with no treatment-related serious adverse events reported. The most commonly reported (>5% overall) adverse events for placebo, 6-week cytisinicline, and 12-week cytisinicline were:

- •Insomnia: (7.6%, 11.0%, 11.9%)
- •Abnormal dreams: (5.7%, 9.1%, 7.7%)
- •Nausea (7.3%, 9.5%, 6.9%)
- •Headache (6.1%, 7.6%, 8.5%)

“The ORCA-3 study findings add to a large body of evidence showing that cytisinicline appears to be a very well-tolerated and effective treatment compared to behavioral support alone for people who are dependent on cigarettes and want to quit,” said Dr. Omer Abid, Board Certified Addiction Medicine Physician & Medical Director of Insight Behavioral Health, Principal Investigator at Insight Research Institute, and ORCA-3 Investigator. “Cytisinicline gives hope for future smoking cessation success, given that there are limited available treatments, and many have tolerability limitations that lead to lack of compliance or adoption.”

The health consequences of smoking are widely known, yet the use of combustible nicotine cigarettes continues to be a global health issue. There are an estimated 28.3 million adults in the United States, and more than 1 billion people globally that currently smoke. Smoking remains the leading cause of preventable death and disease and claims the lives of an estimated 8 million people worldwide each year. If approved, cytisinicline could be the first new prescription treatment in nearly 20 years to help the millions of people who smoke to overcome nicotine dependence.

“Following the success of our previous clinical trials, and years of research, we are thrilled with the results from this second and confirmatory Phase 3 study of cytisinicline. With more than 2,000 clinical trial participants in our ORCA program to date, we are confident that cytisinicline has the potential to help the millions of people who are battling nicotine dependence,” said John Bencich, Chief Executive Officer of Achieve Life Sciences. “We would like to extend our gratitude to the ORCA-3 trial participants, the healthcare providers, and to everyone who continues to support Achieve’s mission of helping people live better and healthier lives. We are excited about the future and continuing our work with regulators with the aim of bringing cytisinicline to market.”

Conference Call Details
Achieve will host a conference call at 8:30 AM EDT today, Tuesday, May 23, 2023. To access the webcast and the accompanying data presentation, visit the investor relations page of the Achieve website at http://ir.achievelifesciences.com/events-and-webcasts. Alternatively, access to the live conference call is available by dialing (877) 269-7756 (U.S. & Canada) or (201) 689-7817 (International) and referencing conference ID 13739070. A webcast replay will be available approximately two hours after the call and will be archived on the website for 90 days.

Further information on cytisinicline and Achieve Life Sciences can be found at www.achievelifesciences.com**.**

About ORCA-3
The Phase 3 ORCA-3 trial evaluated 792 adults who smoked cigarettes on a daily basis at 20 clinical trial locations in the United States. The trial was initiated in January 2022 and completed enrollment in September 2022, with topline results reported in May 2023. ORCA-3 participants received 3mg cytisinicline dosed 3 times daily for either 6 or 12 weeks and were monitored through 24 weeks post randomization. The trial was blinded, placebo-controlled, and all subjects received behavioral support for the duration of the trial. The primary endpoint was biochemically verified continuous abstinence during the last four weeks of treatment. Secondary outcome measures assessed continued abstinence rates through 6 months from the start of study treatment.

About Achieve and Cytisinicline
Achieve's focus is to address the global smoking health and nicotine addiction epidemic through the development and commercialization of cytisinicline. Tobacco use is currently the leading cause of preventable death that is responsible for more than eight million deaths worldwide and nearly half a million deaths in the United States annually.[1,2] More than 87% of lung cancer deaths, 61% of all pulmonary disease deaths, and 32% of all deaths from coronary heart disease are attributable to smoking and exposure to secondhand smoke.[2]

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

Cytisinicline is a plant-based alkaloid with a high binding affinity to the nicotinic acetylcholine receptor. It is believed to aid in treating nicotine addiction for smoking and e-cigarette cessation by interacting with nicotine receptors in the brain, reducing the severity of withdrawal symptoms, and reducing the reward and satisfaction associated with nicotine products. Cytisinicline is an investigational product candidate being developed for the treatment of nicotine addiction and has not been approved by the Food and Drug Administration for any indication in the United States.

Forward Looking Statements
This press release contains forward-looking statements within the meaning of the "safe harbor" provisions of the Private Securities Litigation Reform Act of 1995, including, but not limited to, statements regarding the timing and nature of cytisinicline clinical development, data results and commercialization activities, the potential market size for cytisinicline, the potential benefits, safety and tolerability of cytisinicline, the ability to discover and develop new uses for cytisinicline, including but not limited to as an e-cigarette cessation product, and the development and effectiveness of new treatments. All statements other than statements of historical fact are statements that could be deemed forward-looking statements. Achieve may not actually achieve its plans or product development goals in a timely manner, if at all, or otherwise carry out its intentions or meet its expectations or projections disclosed in these forward-looking statements. These statements are based on management's current expectations and beliefs and are subject to a number of risks, uncertainties and assumptions that could cause actual results to differ materially from those described in the forward-looking statements, including, among others, the risk that cytisinicline may not demonstrate the hypothesized or expected benefits; the risk that Achieve may not be able to obtain additional financing to fund the development of cytisinicline; the risk that

cytisinicline will not receive regulatory approval or be successfully commercialized; the risk that new developments in the smoking cessation landscape require changes in business strategy or clinical development plans; the risk that Achieve's intellectual property may not be adequately protected; general business and economic conditions; risks related to the impact on our business of macroeconomic conditions, including inflation, rising interest rates, instability in the global banking sector, and public health crises, such as the COVID-19 pandemic and the other factors described in the risk factors set forth in Achieve's filings with the Securities and Exchange Commission from time to time, including Achieve's Annual Reports on Form 10-K and Quarterly Reports on Form 10-Q. Achieve undertakes no obligation to update the forward-looking statements contained herein or to reflect events or circumstances occurring after the date hereof, other than as may be required by applicable.

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Glenn.Silver@Finnpartners.com
(646) 871-8485

References

[1] World Health Organization. WHO Report on the Global Tobacco Epidemic, 2019. *Geneva*: World Health Organization, 2017.
[2] U.S. Department of Health and Human Services. The Health Consequences of Smoking – 50 Years of Progress. A Report of the Surgeon General, 2014.
[3] Cornelius ME, Loretan CG, Jamal A, et al. Tobacco Product Use Among Adults – United States, 2021. MMWR Morb Mortal Wkly Rep 2023;72:475–483.
[4]Park Lee E, Ren C, Cooper M, Cornelius M, Jamal A, Cullen KA. Tobacco Product Use Among Middle and High School Students – United States, 2022. Morbidity and Mortality Weekly Report, 2022; 71:45.

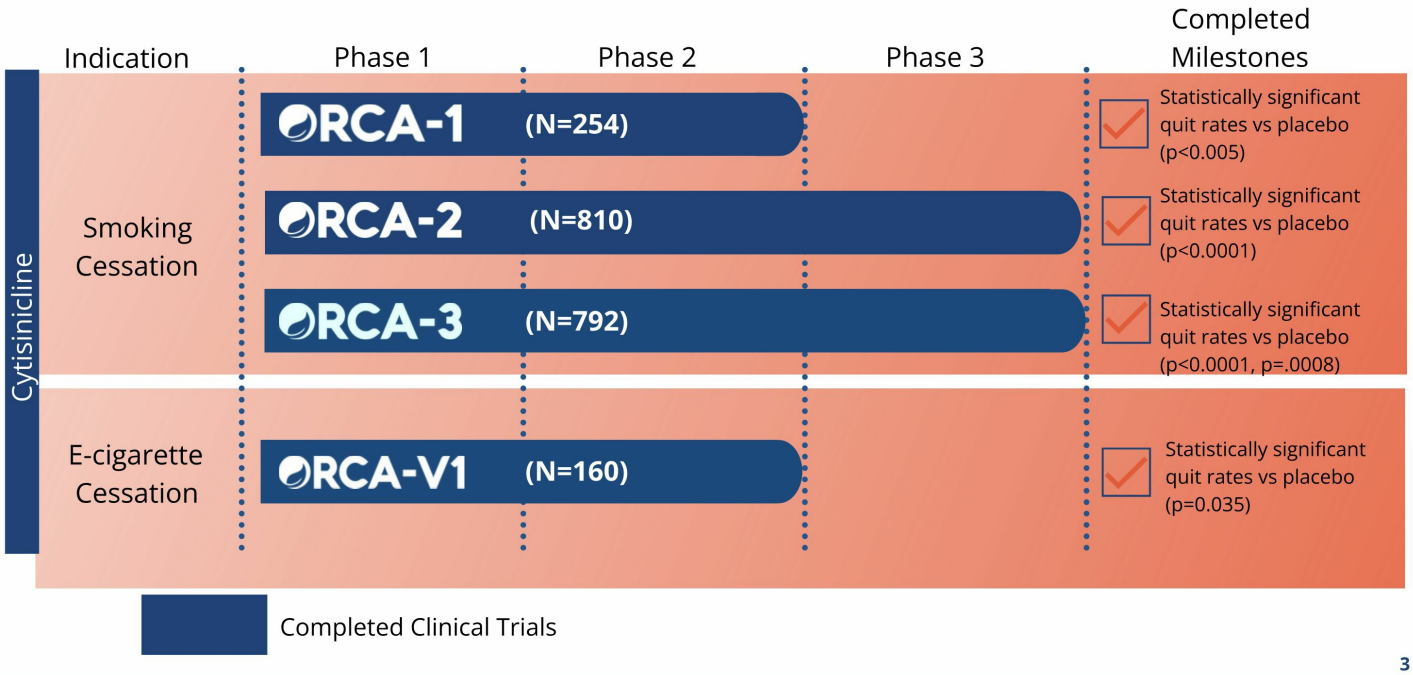
Exhibit 99.2


ACHIEVE
LIFE SCIENCES
ORCA-3 Phase 3 Topline Data
NASDAQ: ACHV | May 23, 2023

Forward Looking Statements

This presentation contains forward-looking statements, including, but not limited to, statements regarding the timing of planned clinical development activities of cytisinicline; the projected path toward potential regulatory approval; the safety, efficacy and commercial potential of cytisinicline; the potential market for cytisinicline; the benefits of cytisinicline relative to competitors; the anticipated benefits of cytisinicline; plans, objectives, expectations and intentions with respect to future operations. All statements other than statements of historical fact are statements that could be deemed forward-looking statements. Achieve Life Sciences, Inc. ("we," "us," "our," or "the Company") may not actually achieve its plans or product development goals in a timely manner, if at all, or otherwise carry out the intentions or meet the expectations or projections disclosed in these forward-looking statements. These statements are based on management's current expectations and beliefs and are subject to a number of risks, uncertainties and assumptions that could cause actual results to differ materially from those described in the forward-looking statements, including, among others, general business and economic conditions, including inflation, rising interest rates, instability in the global banking sector and risks related to the COVID-19 pandemic or similar public health crisis; risks related to the Russian military action in Ukraine; the need for and ability to obtain additional financing; the risk that cytisinicline may not demonstrate the hypothesized or expected benefits; the risk that cytisinicline will not receive regulatory approval or be successfully commercialized; the risk that new developments in the smoking cessation landscape require changes in business strategy or clinical development plans; the risk that the Company's intellectual property may not be adequately protected; other risks associated with the process of developing, obtaining regulatory approval for and commercializing drug candidates that are safe and effective for use as human therapeutics; and the other factors described in the risk factors set forth in the Company's filings with the Securities and Exchange Commission from time to time, including its Annual Reports on Form 10-K and Quarterly Reports on Form 10-Q. The Company undertakes no obligation to update the forward-looking statements contained herein or to reflect events or circumstances occurring after the date hereof, other than as may be required by applicable law.

ORCA Development Program



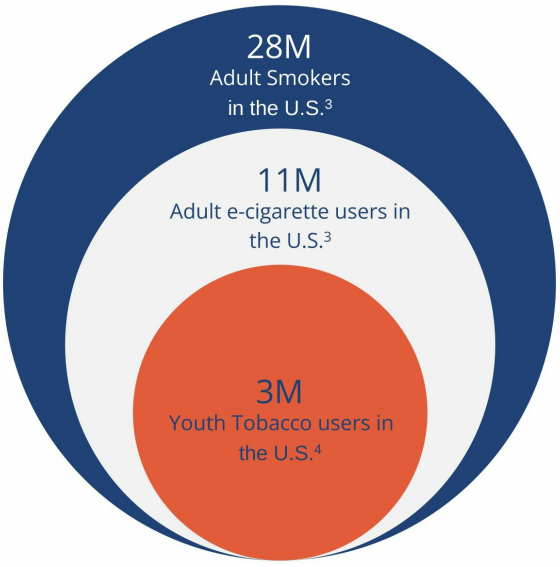
Large Market Opportunity: Treating Nicotine Addiction

Tobacco use is the leading cause of preventable death[1]

1.1B
Global Smokers[1]

~480K
Deaths in the U.S. annually[2]

$300B
Annualized healthcare costs associated with smoking costs in the U.S.[2]



1. World Health Organization (WHO). WHO Report on the Global Tobacco Epidemic, 2019.
2. U.S. Department of Health and Human Services, The Health Consequences of Smoking, 50 Years of Progress: A Report of the Surgeon General, 2014.
3. Cornelius ME, Loretan CG, Jamal A, et al. Tobacco Product Use Among Adults – United States, 2021. MMWR Morb Mortal Wkly Rep 2023;72:475–483.
4. Park-Lee E, Ren C, Cooper M, Cornelius M, Jamal A, Cullen KA. Tobacco Product Use Among Middle and High School Students - United States, 2022. MMWR Morb Mortal Wkly Rep. 2022 Nov 11;71(45):1429-1435.

ORCA-3: Phase 3 Topline Results

May 2023

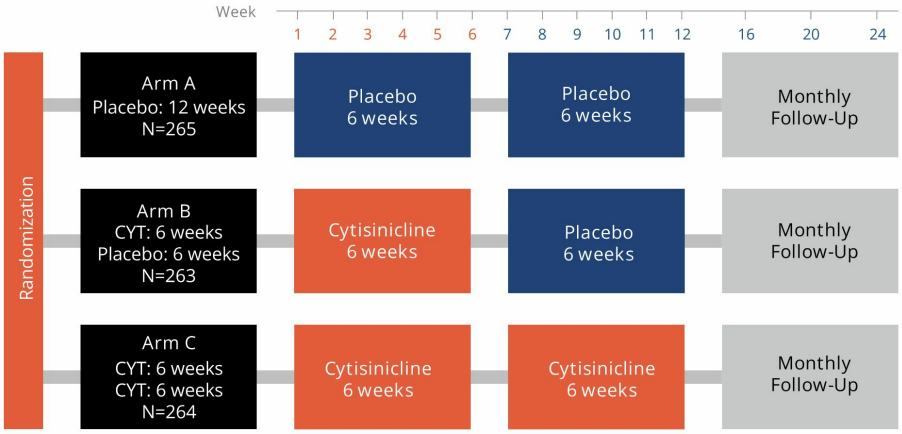
ORCA-3: Phase 3 Study Design (N=792)

Objective:

- Evaluate safety and efficacy of 3.0 mg of cytisinicline vs placebo administered TID over 6 & 12 weeks
- All subjects received standardized behavioral support and will be followed up to 24 weeks

Population:

- Smokers of 10 cigarettes/day and expired air CO > 10 ppm



Multiple Primary Endpoints:

- Biochemically verified smoking cessation during the last 4 weeks of treatment
  - Arm B: Weeks 3-6
  - Arm C: Weeks 9-12

Secondary Endpoint:

- Continuous smoking cessation from end of treatment through 6 months

Statistics:

- >95% power for the 24-week comparisons

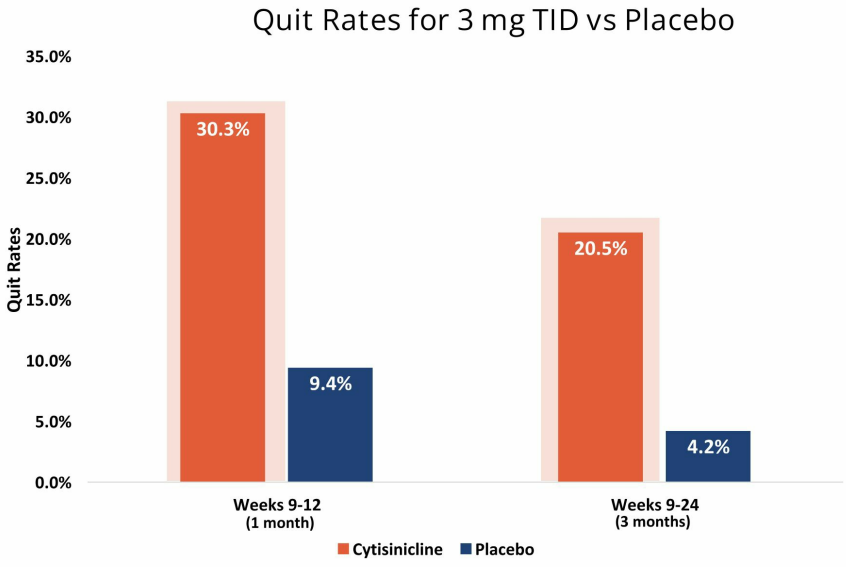
ORCA-3

ORCA-3 Demographics and Baseline Characteristics

Characteristic	Randomized (N=792)
Sex	
Female	439 (55%)
Male	353 (45%)
Race	
White	631 (80%)
Black or African American	139 (18%)
Other	21 (2%)
Age (yrs)	
Median	53
Average # Daily Cigarettes in last 30 days	
Median	20
Duration of Smoking Years	
Median	36
# of Previous Quit Attempts	
Median	4

12-week Cytisinicline Treatment:

4x increased likelihood of smoking cessation at end of treatment & ~6x more likely at 24 weeks



Primary Endpoint:
Weeks 9-12 Odds Ratio

4.40 (p<0.0001)

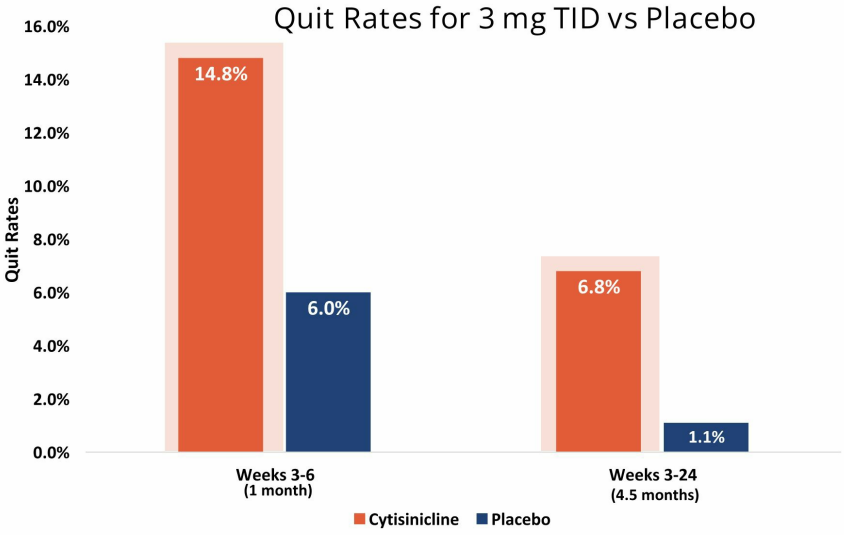
Secondary Endpoint:
Weeks 9-24 Odds Ratio

5.79 (p<0.0001)

ORCA-3

6-week Cytisinicline Treatment:

~3x increased likelihood of smoking cessation at end of treatment & 6x more likely at 24 weeks



Primary Endpoint:
Weeks 3-6 Odds Ratio

2.85 (p=0.0008)

Secondary Endpoint:
Weeks 3-24 Odds Ratio

6.25 (p=0.0006)

ORCA-3

Safety Profile:
Well-tolerated with low rates of adverse events reported

Most commonly reported AE's (>5% Overall)

Adverse Event (AE)	Placebo (N=262)	6-week CYT (N=263)	12-week CYT (N=260)
At least 1 TEAE	164 (62.6%)	170 (64.6%)	168 (64.5%)
Insomnia	20 (7.6%)	29 (11.0%)	31 (11.9%)
Abnormal Dreams	15 (5.7%)	24 (9.1%)	20 (7.7%)
Nausea	19 (7.3%)	25 (9.5%)	18 (6.9%)
Headache	16 (6.1%)	20 (7.6%)	22 (8.5%)

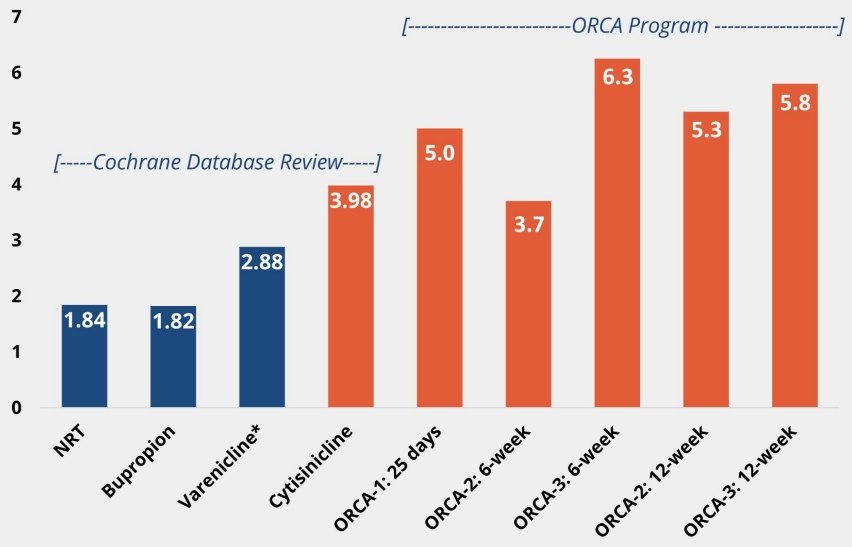
No treatment-related serious adverse events reported

ORCA-3

Strong Relative Efficacy Compared to Current Treatments

- Odds Ratio (OR) expresses the drug effect in proportion to placebo
- OR is the preferred outcome measure in smoking cessation trials in the literature

Odds Ratios (OR) vs Placebo at Longest Follow-up



*Varenicline = Chantix

1. Cahill K et al; The Cochrane Library 2013, Issue 5 (For NRT, Bupropion and Varenicline)
2. Cahill K et al; Cochrane Database of Systematic Reviews 2016, Issue 5
3. ORCA-1 publication in NTR for 3mg TID arm weeks 5-8
4. ORCA-2 and ORCA-3 Odds Ratios at the longest follow up (weeks 9-24) for 3mg TID dosing

Cytisinicline is Well Positioned...

To Meet the Cessation Needs of Smokers and Patients Battling Nicotine Addiction

Safe & Well-Tolerated
Dual-acting, differentiated, and highly selective MOA provides minimal adverse events (AEs) and excellent compliance rates

Efficacious
Robust efficacy demonstrated in multiple, large, randomized controlled trials

Short Course of Treatment
6-week treatment with option to extend to 12 weeks for extended benefit

Positive In-Market Experience
Positive patient & HCP perceptions with no product history of black-box warnings or suicidality

Naturally Derived Therapy
Sourced from plant-based material which is appealing to specific patient populations

Clear Path to Market
Collaborative engagement with FDA on NDA-required activities and Affordable Care Act mandates coverage of approved smoking cessation products

APPENDIX

ORCA-2: Phase 3 Study Results

April 2022

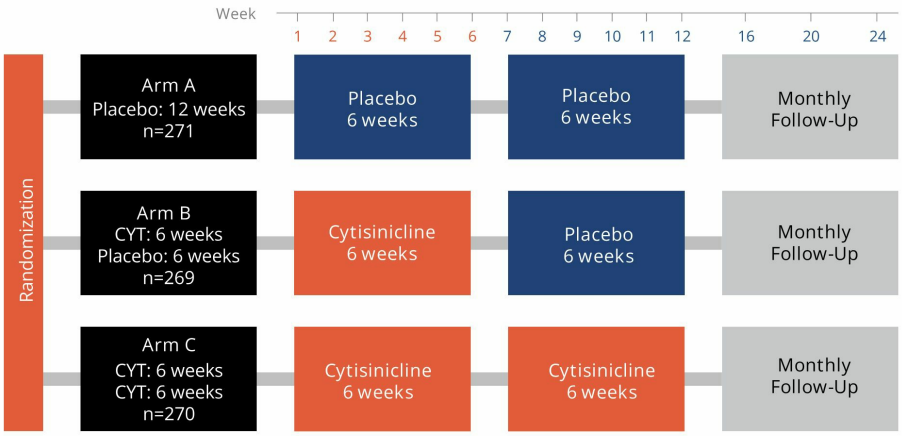
ORCA-2: Phase 3 Study Design (N=810)

Objective:

- Evaluate safety and efficacy of 3.0 mg of cytisinicline vs placebo administered 3x daily (TID) for 6 & 12 weeks
- All subjects received standard behavioral support and were followed out to 24 weeks

Population:

- Smokers of 10 cigarettes/day and expired air CO > 10 ppm



Multiple Primary Endpoints:

- Biochemically verified continuous abstinence during the last 4 weeks of treatment
  - Arm B: Weeks 3-6
  - Arm C: Weeks 9-12

Secondary Endpoint:

- Continuous abstinence from end of treatment through week 24

Statistics:

- >95% power for the 24-week comparisons

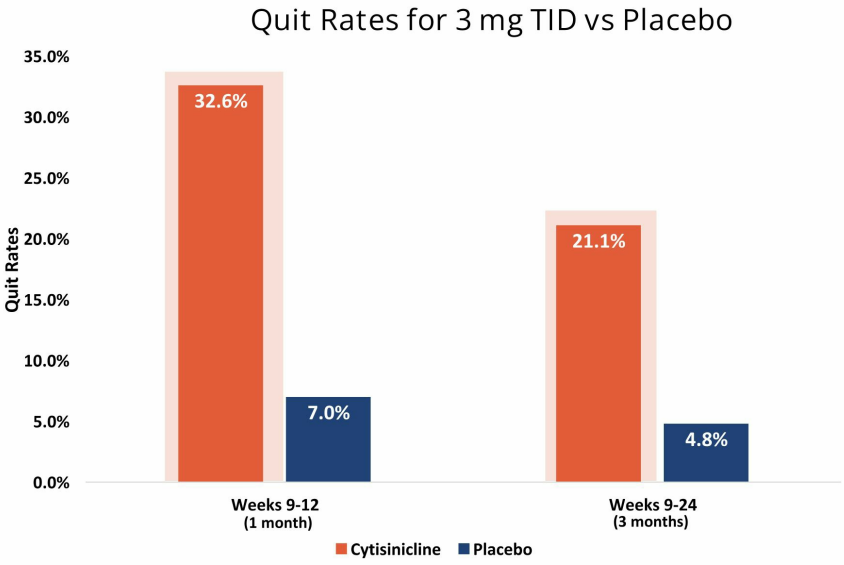
ORCA-2

ORCA-2: Demographics and Baseline Characteristics

Characteristic	Randomized (N=810)
Sex	
Female	442 (55%)
Male	368 (45%)
Race	
White	659 (81%)
Black or African American	130 (16%)
Other	21 (3%)
Age (yrs)	
Median	54
Average # Daily Cigarettes in last 30 days	
Median	20
Duration of Smoking Years	
Median	38
# of Previous Quit Attempts	
Median	4

12-week Cytisinicline Treatment:

6.3x increased likelihood of cessation at end of treatment



Primary Endpoint:
Weeks 9-12 Odds Ratio

6.3 (p<0.0001)

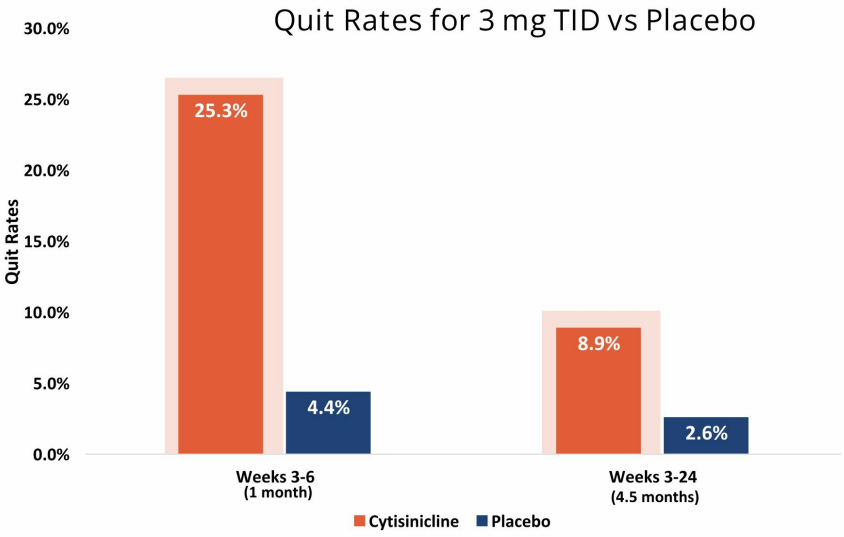
Secondary Endpoint:
Weeks 9-24 Odds Ratio

5.3 (p<0.0001)

ORCA-2

6-week Cytisinicline Treatment:

8x increased likelihood of cessation at end of treatment



Primary Endpoint:
Weeks 3-6 Odds Ratio

8.0 (p<0.0001)

Secondary Endpoint:
Weeks 3-24 Odds Ratio

3.7 (p=0.0016)

ORCA-2

Safety Profile:
Well-tolerated with single digit rates of adverse events

Most commonly reported AE's (>5% Overall)

Adverse Event (AE)	Placebo (N=270)	6-week CYT (N=269)	12-week CYT (N=270)
At least 1 TEAE	166 (61.5%)	172 (63.9%)	184 (68.1%)
Insomnia	13 (4.8%)	23 (8.6%)	26 (9.6%)
Abnormal Dreams	8 (3.0%)	22 (8.2%)	21 (7.8%)
Headaches	22 (8.1%)	18 (6.7%)	21 (7.8%)
Nausea	20 (7.4%)	16 (5.9%)	15 (5.6%)

No treatment-related serious adverse events reported

ORCA-2

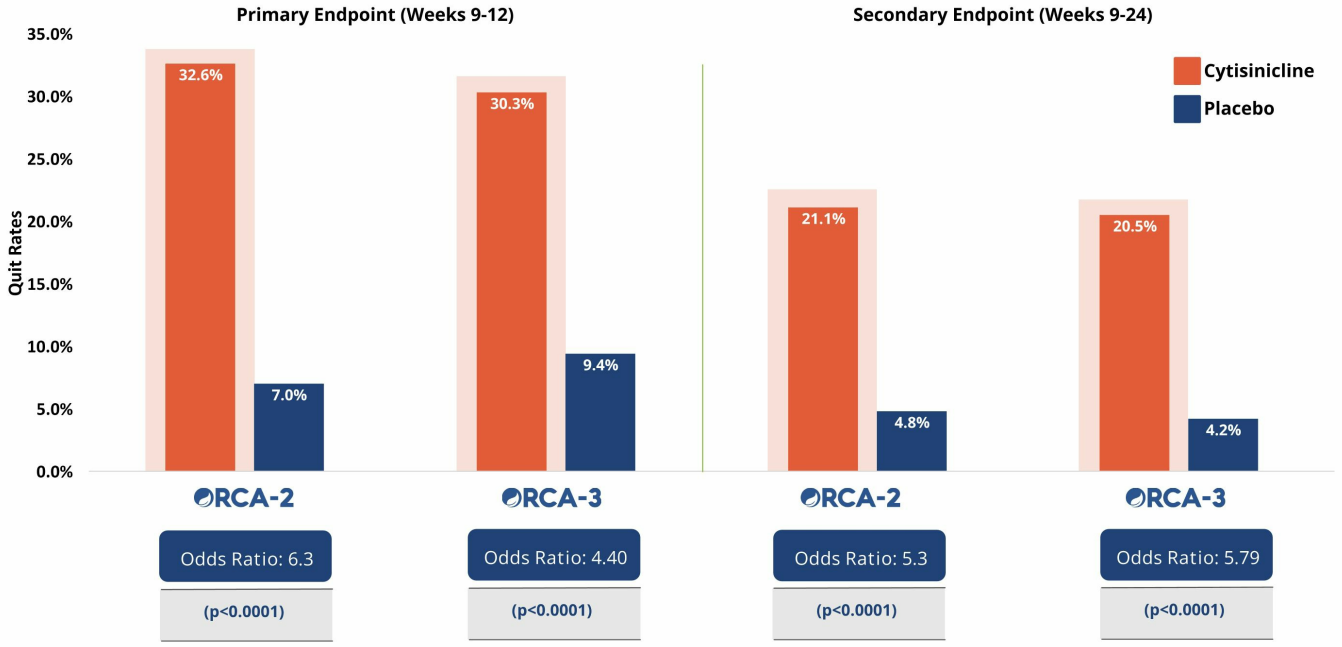
ORCA-2 & ORCA-3
Combined Results

ORCA-2 and ORCA-3 Demographics and Baseline Characteristics

Characteristic	ORCA-2 Randomized (N=810)	ORCA-3 Randomized (N=792)
Sex		
Female	442 (55%)	439 (55%)
Male	368 (45%)	353 (45%)
Race		
White	659 (81%)	631 (80%)
Black or African American	130 (16%)	139 (18%)
Other	21 (3%)	21 (2%)
Age (yrs)		
Median	54	52
Average # Daily Cigarettes in last 30 days		
Median	20	20
Duration of Smoking Years		
Median	38	36
# of Previous Quit Attempts		
Median	4	4

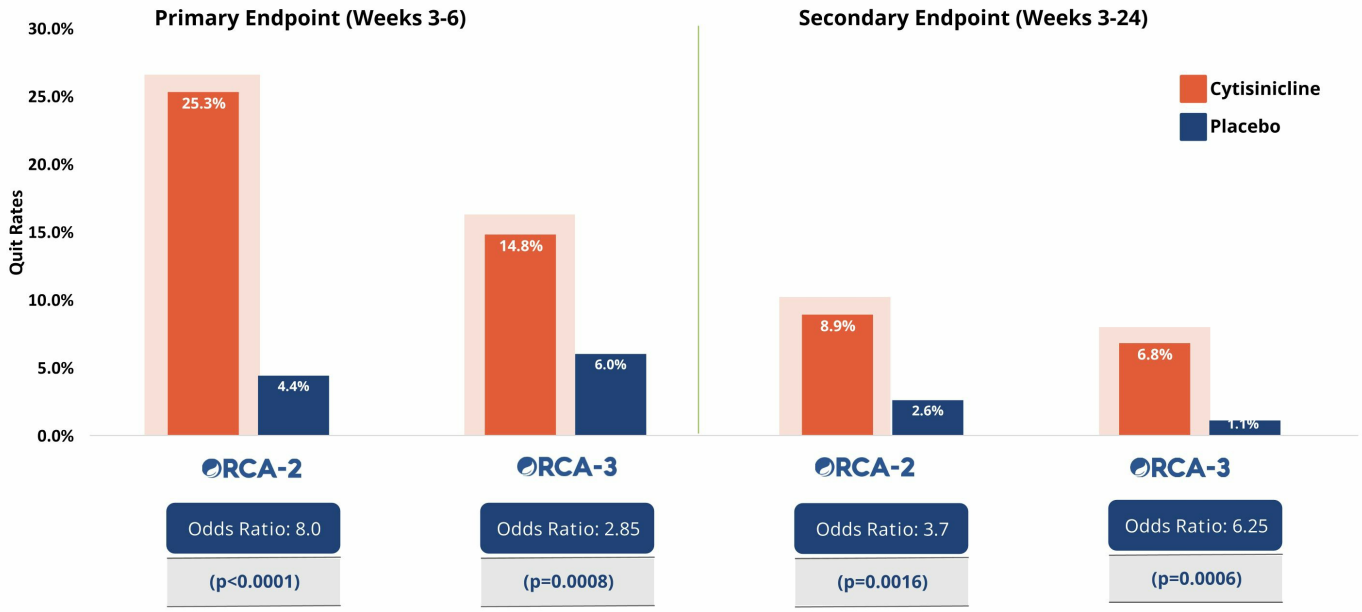
12-week Cytisinicline Treatment:

ORCA-2 (N=810) and ORCA-3 (N=792)



6-week Cytisinicline Treatment:

ORCA-2 and ORCA-3



Safety Profile:
Well-tolerated with low rates of adverse events reported

Most commonly reported AE's (>5% Overall)

Adverse Event (AE)	Placebo		6-week CYT		12-week CYT	
	ORCA-2	ORCA-3	ORCA-2	ORCA-3	ORCA-2	ORCA-3
At least 1 TEAE	166 (61.5%)	164 (62.6%)	172 (63.9%)	170 (64.6%)	184 (68.1%)	168 (64.5%)
Insomnia	13 (4.8%)	20 (7.6%)	23 (8.6%)	29 (11.0%)	26 (9.6%)	31 (11.9%)
Abnormal Dreams	8 (3.0%)	15 (5.7%)	22 (8.2%)	24 (9.1%)	21 (7.8%)	20 (7.7%)
Nausea	20 (7.4%)	19 (7.3%)	16 (5.9%)	25 (9.5%)	15 (5.6%)	18 (6.9%)
Headache	22 (8.1%)	16 (6.1%)	18 (6.7%)	20 (7.6%)	21 (7.8%)	22 (8.5%)

No treatment-related serious adverse events reported