TOPS Seminar – July 24, 2024

Cytisine for Tobacco Cessation

New Trials and Next Steps for a New/Old Drug

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Disclosures – Nancy Rigotti, MD

- Funding for the two papers presented today
  - Achieve Life Sciences & NIDA
- Funding for tobacco research in past 10 years
  - NIH: NCI, NHLBI, NIDA, NIMH
  - Pharmaceutical: Achieve Life Sciences, Pfizer
  - None from manufacturers of tobacco or e-cigarette products

Current Tobacco Cessation Medications

- FDA-approved products *(3 drugs)*
  - Nicotine replacement products (patch, gum, lozenge, nasal spray, inhaler)
  - Bupropion
  - Varenicline

- Effectiveness and availability of smoking cessation medications is limited.
  - Medications do not help every smoker.
  - Medications have side effect, cost, and availability issues that limit use.
  - No medications have been approved by US FDA since 2006.

➢ New options are needed.

Cytisine

- Plant-based alkaloid - Golden Rain (*Cytisus laburnum*) native to Europe
- Similar mechanism of action as varenicline.
  - Partial agonist at $\alpha 4\beta 2$ nicotinic acetylcholine receptors.
- Low-cost generic smoking cessation aid used in Eastern and Central Europe for decades.
  - Sopharma, Bulgaria (Tabex®)
  - Aflofarm, Poland (Desmoxan®)

- Modern clinical trial evidence of efficacy and safety began in 2011
- Canada: approved as a natural product (Craav®) in 2017
- UK: approved as a medication in January 2024

Golden Rain (Cytisus laburnum)

Clinical Trials of Cytisine: Efficacy and Safety

N Engl J Med 2011;365:1193

ORIGINAL ARTICLE

Placebo-Controlled Trial of Cytisine for Smoking Cessation

Robert West, Ph.D., Witold Zatonski, M.D., Magdalena Cedzynska, M.A., Dorota Lewandowska, Ph.D., M.D., Joanna Pazik, Ph.D., M.D., Paul Aveyard, Ph.D., M.D., and John Stapleton, M.Sc.

- Poland: cytisine vs. placebo
- Quit for 12 mo: cytisine 8.4%, placebo 2.4%

  (RR 3.4, 95% CI 1.7-7.1)

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 18, 2014 VOL. 371 NO. 25

Cytisine versus Nicotine for Smoking Cessation

Natalie Walker, Ph.D., Colin Howe, Ph.D., Marewa Glover, Ph.D., Hayden McRobbie, M.B., Ch.B., Ph.D., Joanne Barnes, Ph.D., Vili Nosa, Ph.D., Varsha Parag, M.Sc., Bruce Bassett, B.A., and Christopher Bullen, M.B., Ch.B., Ph.D.

- New Zealand*:* cytisine vs. nicotine patch
- Quit for 6 mo: cytisine 22%, patch 15%

  (RR 1.4, 95% CI 1.1-1.8)

The NEW ENGLAND JOURNAL of MEDICINE

EDITORIALS

Dec. 18, 2014

Cytisine — A Tobacco Treatment Hiding in Plain Sight

Nancy A. Rigotti, M.D.

- Could it be an effective new medication for smoking cessation?
- Is it like varenicline but a drug that smokers are not reluctant to take?
- Could it be an affordable, accessible drug to help the world's smokers?
  - Challenge for the USA:
    - How can a generic medication get FDA approval?
    - And, if so, how can it stay low in cost?

Cytisine → Cytisinicline

Achieve Life Sciences is developing this drug for smoking cessation

- Using cytisine from Bulgaria (Tabex)
- Renamed cytisinicline *(USAN* name for a generic product)*
- Conducting a full drug development program
  - Pre-clinical studies were partly funded by NIH (NCCIH)
  - IND awarded by FDA in 2017

** **United States Adopted Name**, a nonproprietary designation for any compound used as a drug, established by negotiation between its manufacturer and a council sponsored jointly by the American Medical Association, American Pharmaceutical Association, and United States Pharmacopeial Convention, Inc.*

Cytisinicline clinical trials

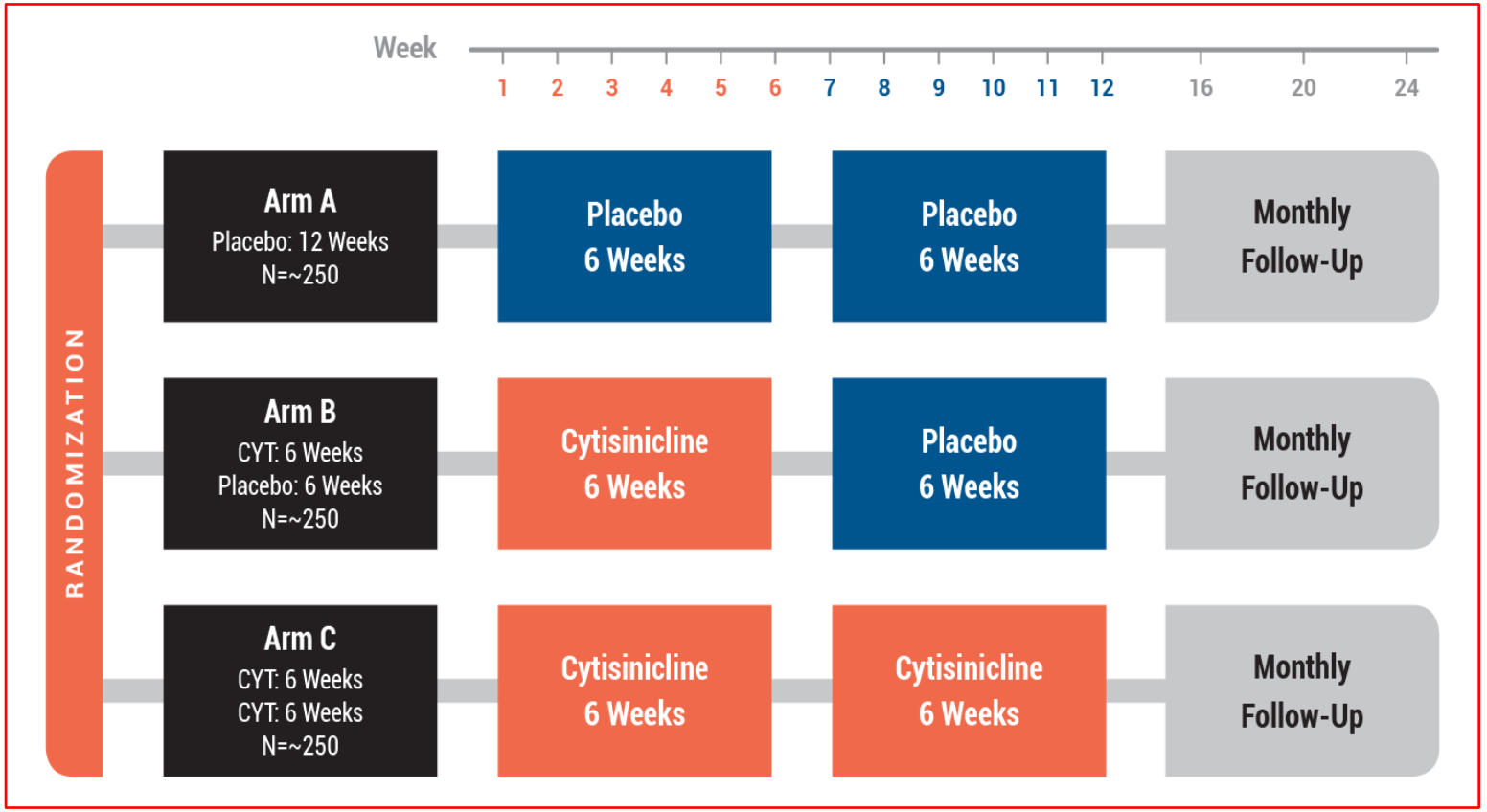
- First goal: Define optimal treatment regimen *(dose, frequency, duration)*
  - Traditional = 25-day downward titration using 1.5 mg tablets (6 doses/day→1/day)
  - Pharmacokinetic studies support dosing 3 times/day (TID)
  - Phase 2b RCT supports a simpler regimen: a higher dose (3 mg TID) for 25 days*
- Next goal: Demonstrate effectiveness and safety in a U.S. sample
  - 2 Phase 3 RCTs tested smoking cessation efficacy of 6 or12 weeks of this regimen**

* Nides M *et al. Nicotine Tob Res* 2021; 23:1656. ** Rigotti NA *et al. JAMA.* 2023;330:152 and www.achievelifesciences.com

ORCA 2: Phase 3 Randomized Clinical Trial

- **AIM:** Test the efficacy and safety of a longer course of the new cytisinicline regimen, with behavioral support, vs. placebo
  - 6 weeks vs. placebo
  - 12 weeks vs placebo

- **STUDY DESIGN**
  - Double-blind RCT
  - 3 arm trial
  - All: one pill TID x12 weeks
  - All: behavioral support
  - All followed for 24 weeks
  - 2/3 received active drug



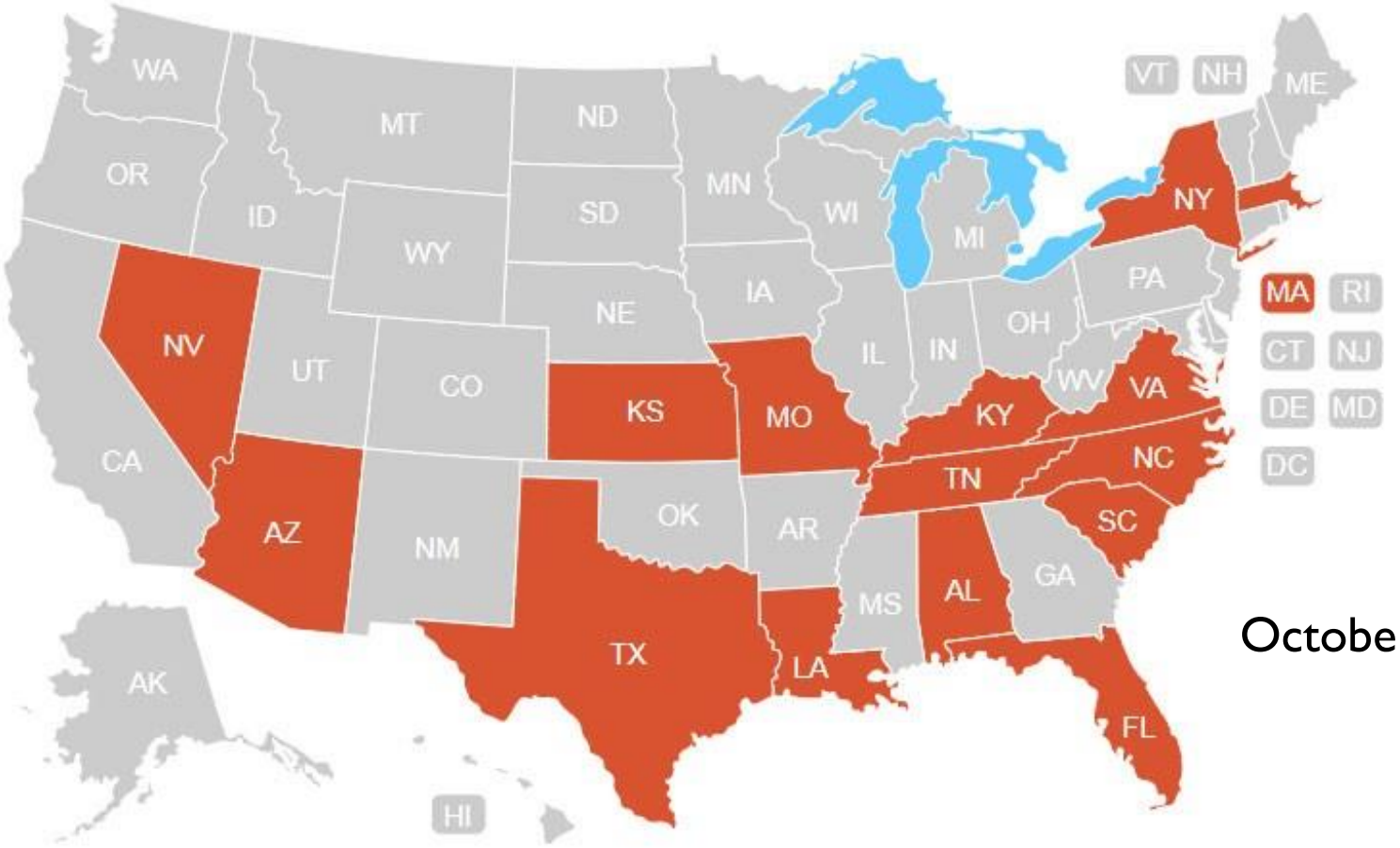
ORCA-2: Inclusion Criteria

- Age ≥18 years
- Cigarette smoker: ≥10 cigarettes per day AND expired air CO ≥10 ppm
  - No other tobacco product use in past 2 weeks
- Willing to set a quit date 5-7 days after randomization.
- Medically and psychiatrically stable
  - No recent acute cardiovascular event or hospitalization
  - No schizophrenia, bipolar disorder, psychosis, suicidal ideation, or mod/severe depression
  - Negative urine drug screen (not tested for cannabis)

ORCA-2: Outcomes

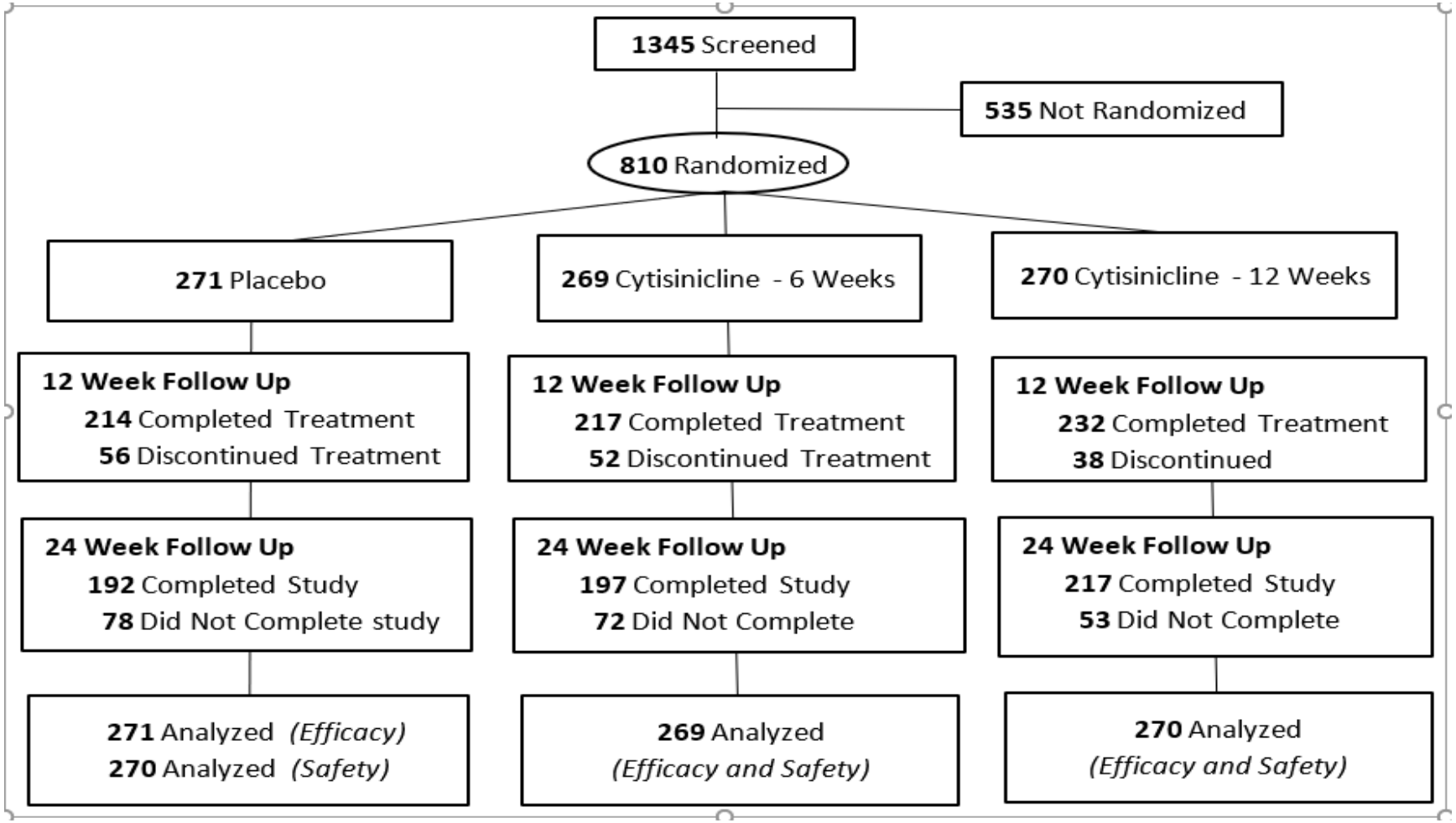
- **PRIMARY ENDPOINTS**
  - Biochemically verified continuous abstinence in the last 4 weeks of treatment (CO<10ppm)
    - 6-week arm: Weeks 3-6 vs. placebo | 12-week arm: Weeks 9-12 vs. placebo
- **SECONDARY ENDPOINT**
  - Continued abstinence from last 4 weeks of treatment through Week 24
- **SAFETY**
  - Adverse events, serious adverse events (#, severity, and attributability to study drug)
- **Analysis**
  - Intent to treat. Assume that missing = smoking

ORCA-2: Participating Sites (N=17)



Enrollment
October 2020 – June 2021

ORCA-2: CONSORT Diagram



810 participants

82% completed 12 weeks

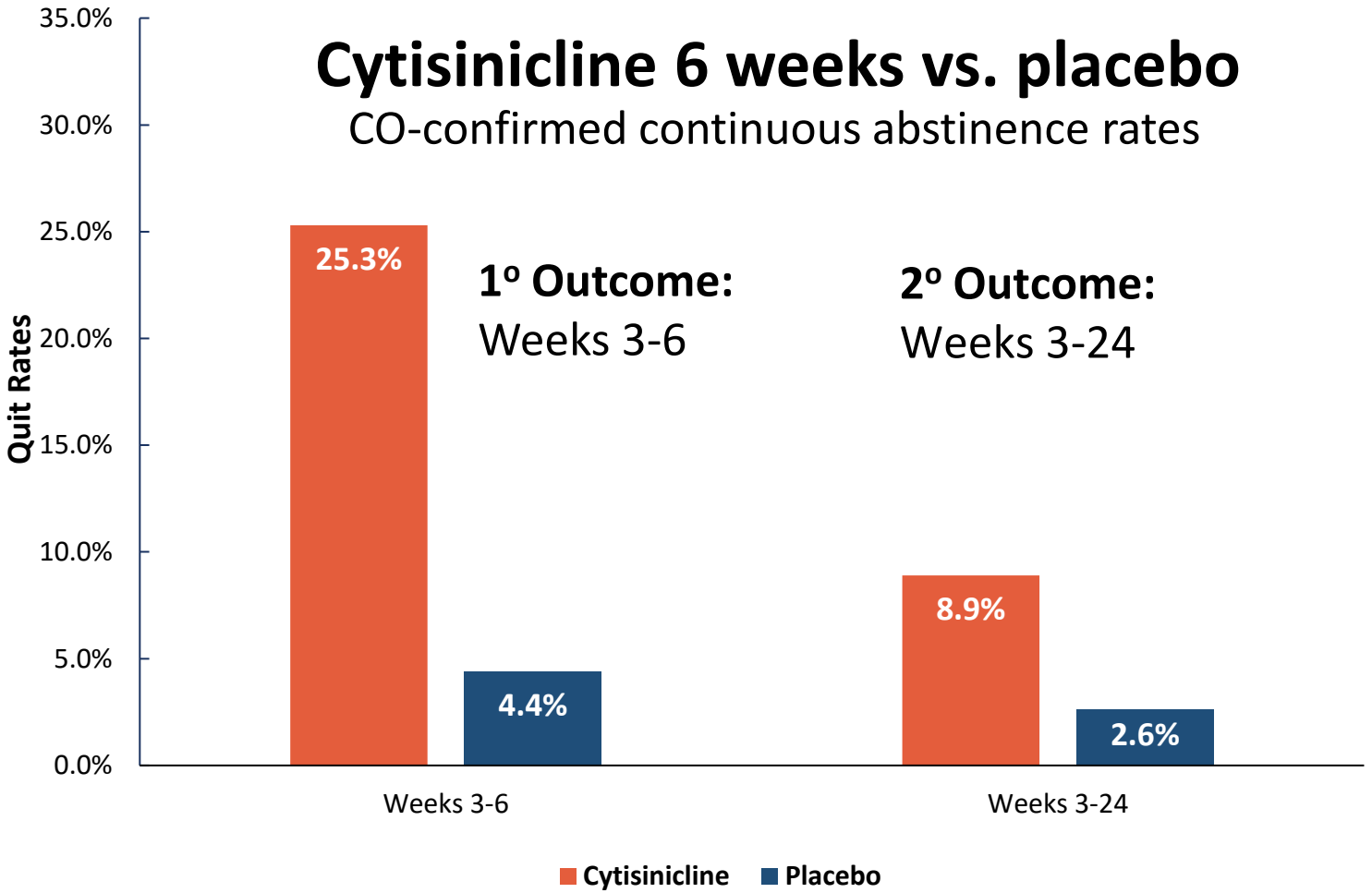
76% followed 24 weeks

Intention-to-treat analysis

ORCA-2: Study Participants, by Group

	Placebo N=271		Cytisinicline 6 weeks N=269		Cytisinicline 12 weeks N=270	
Demographics	**n/mean**	**% / SD**	**n/mean**	**% / SD**	**n/mean**	**% / SD**
Age (mean years, SD)	52.0	12.0	52.2	11.2	53.3	11.6
Female sex – n (%)	159	59%	148	55%	135	50%
Race – n (%)						
Black or African American	42	15%	40	15%	48	18%
White	221	81%	222	82%	216	80%
Another	8	3%	7	3%	6	2%
Hispanic ethnicity-- n (%)	19	7%	26	10%	23	8%
Tobacco use						
Cigarettes per day, past 30 days (mean, SD)	19.4	7.7	19.4	7.3	19.4	7.2
Quitting history						
Prior quit attempts (mean, SD)	5.7	6.8	6.4	10.1	5.6	5.8
Prior cessation medication used - n (%)						
Nicotine replacement product (any)	171	63%	167	62%	174	64%
E-cigarettes	57	21%	60	22%	64	24%
Bupropion	56	21%	40	15%	57	21%
Varenicline	114	42%	113	42%	127	47%

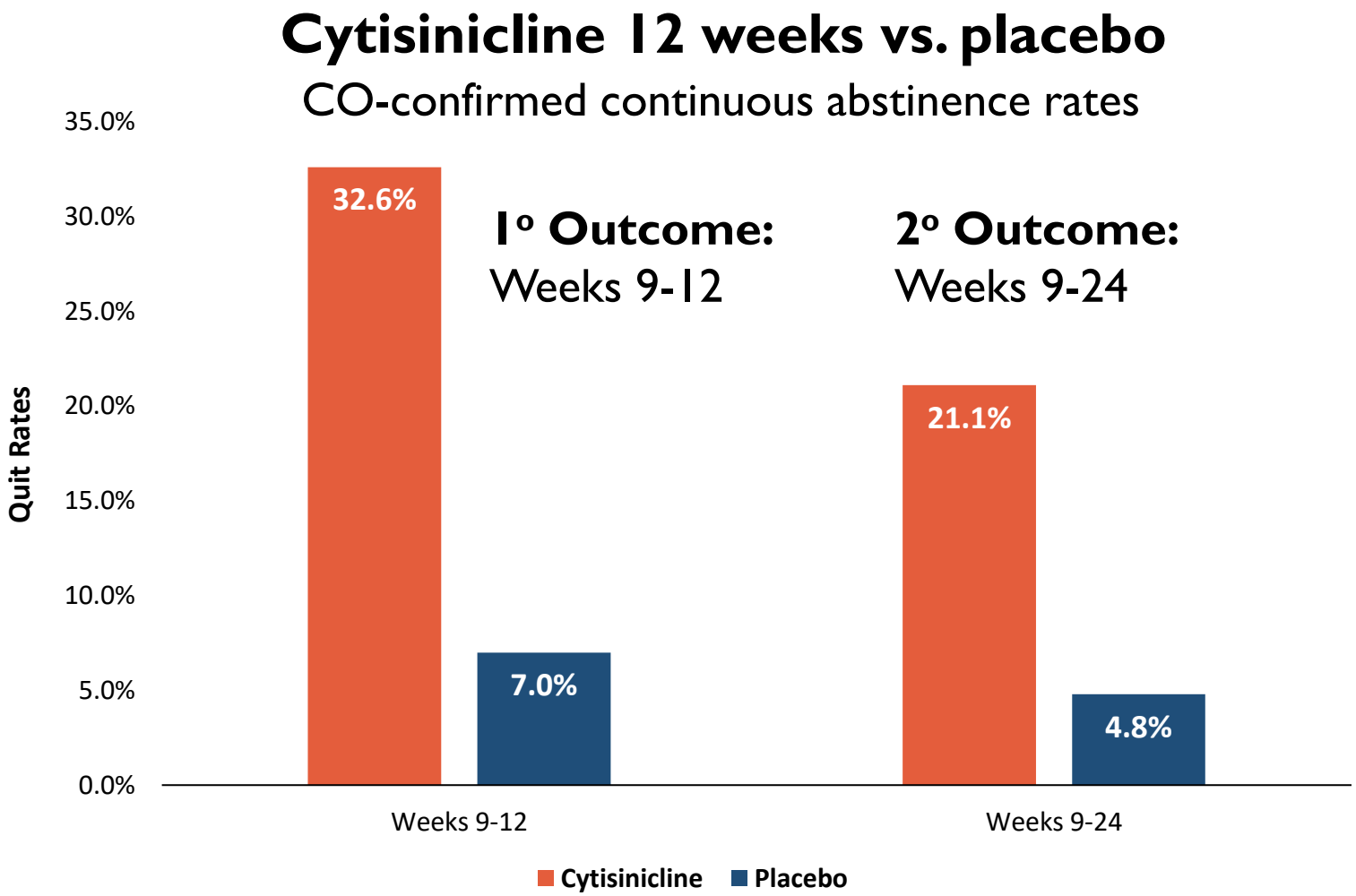
Smoking Cessation Outcomes: Cytisinicline for 6 weeks



Primary Endpoint: Weeks 3-6
OR 8.0 (95% CI: 3.9 - 16.3) p<0.0001

Secondary Endpoint: Weeks 3-24
OR 3.7 (95% CI: 1.5-10.2) p=0.0016

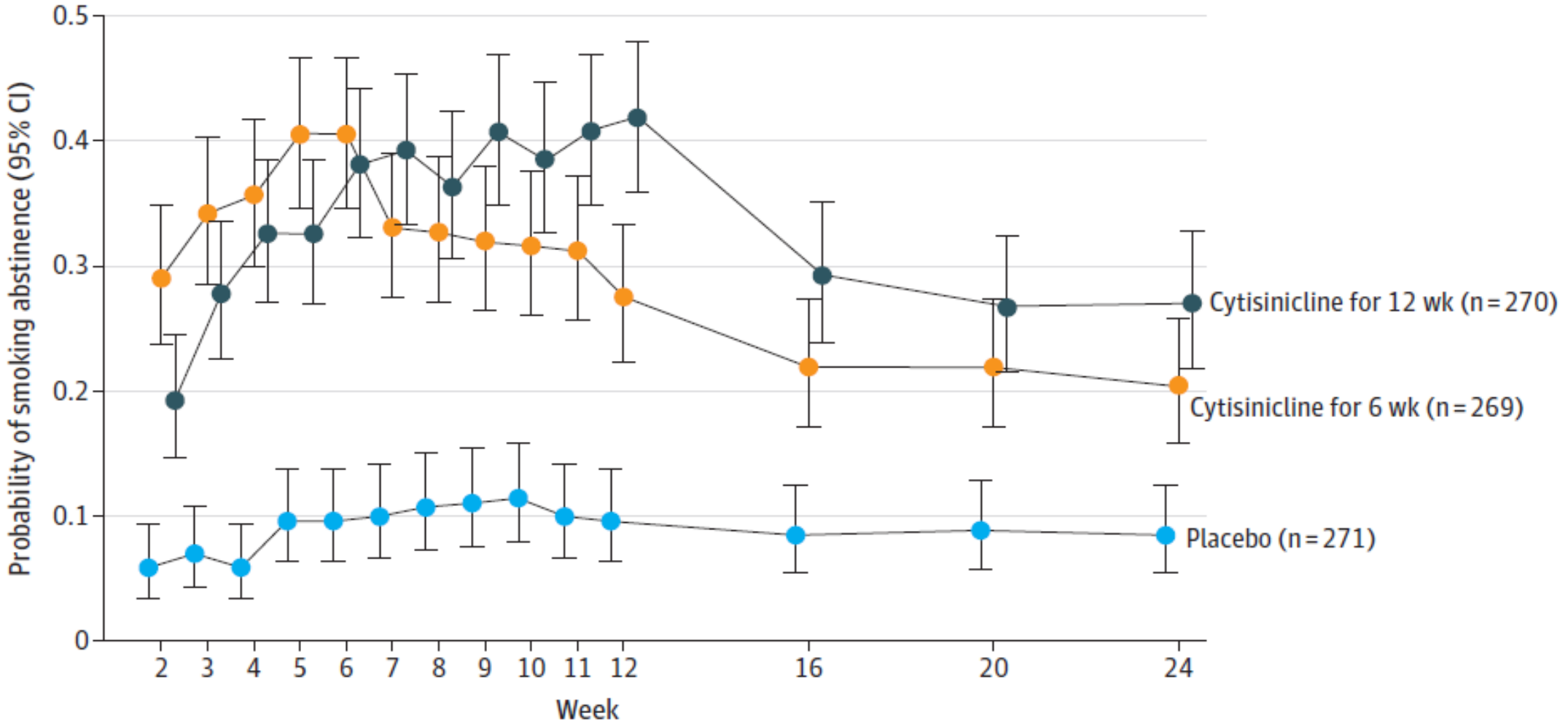
Smoking Cessation Outcomes: Cytisinicline for 12 weeks



Primary Endpoint: Weeks 9-12
OR 6.3 (95% CI: 3.7 - 11.6) p<0.0001

Secondary Endpoint: Weeks 9-24
OR 5.3 (95% CI: 2.8 – 11.1) P<0.0001

Figure 2. Weekly Prevalence Probabilities of Biochemically Confirmed Tobacco Abstinence by Group



ORCA-2: Adverse Events, by Treatment Group

Outcome Measure	Placebo N=270		Cytisinicline 6 weeks N=269		Cytisinicline 12 weeks N=270	
	n	%	n	%	n	%
Participants with any serious adverse event	3	1.1%	10	3.7%	8	3.0%
Treatment emergent adverse events	359	--	459	--	494	--
Mild	239	66.6%	290	63.2%	303	61.3%
Moderate	114	31.8%	148	32.2%	178	36.0%
Severe	6	1.7%	21	4.6%	13	2.6%
Most common adverse events						
Insomnia	13	4.8%	23	8.6%	26	9.6%
Abnormal dreams	8	3.0%	22	8.2%	21	7.8%
Headache	22	8.1%	18	6.7%	21	7.8%
Nausea	20	7.4%	16	5.9%	15	5.6%
Anxiety	5	1.9%	7	2.6%	15	5.6%

No treatment-related serious adverse events were reported

ORCA-2: Limitations

- Limited number of non-White or Hispanic participants
- Exclusion of individuals with serious CVD, psychiatric illness and current illicit substance use
- All subjects received behavioral support for 12 weeks

JAMA | Original Investigation

JAMA. 2023;330(2):152-160. doi:10.1001/jama.2023.10042

Cytisinicline for Smoking Cessation
A Randomized Clinical Trial

Nancy A. Rigotti, MD; Neal L. Benowitz, MD; Judith Prochaska, PhD; Scott Leischow, PhD; Mitchell Nides, PhD; Brent Blumenstein, PhD; Anthony Clarke, PhD; Daniel Cain, BS; Cindy Jacobs, PhD, MD

IMPORTANCE Cytisinic
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Conclusions

This phase 3, multisite, placebo-controlled, randomized clinical trial, the first large trial conducted in the US, demonstrated that a novel regimen of cytisinicline, along with behavioral support, has robust efficacy and excellent tolerability as a treatment for tobacco dependence.

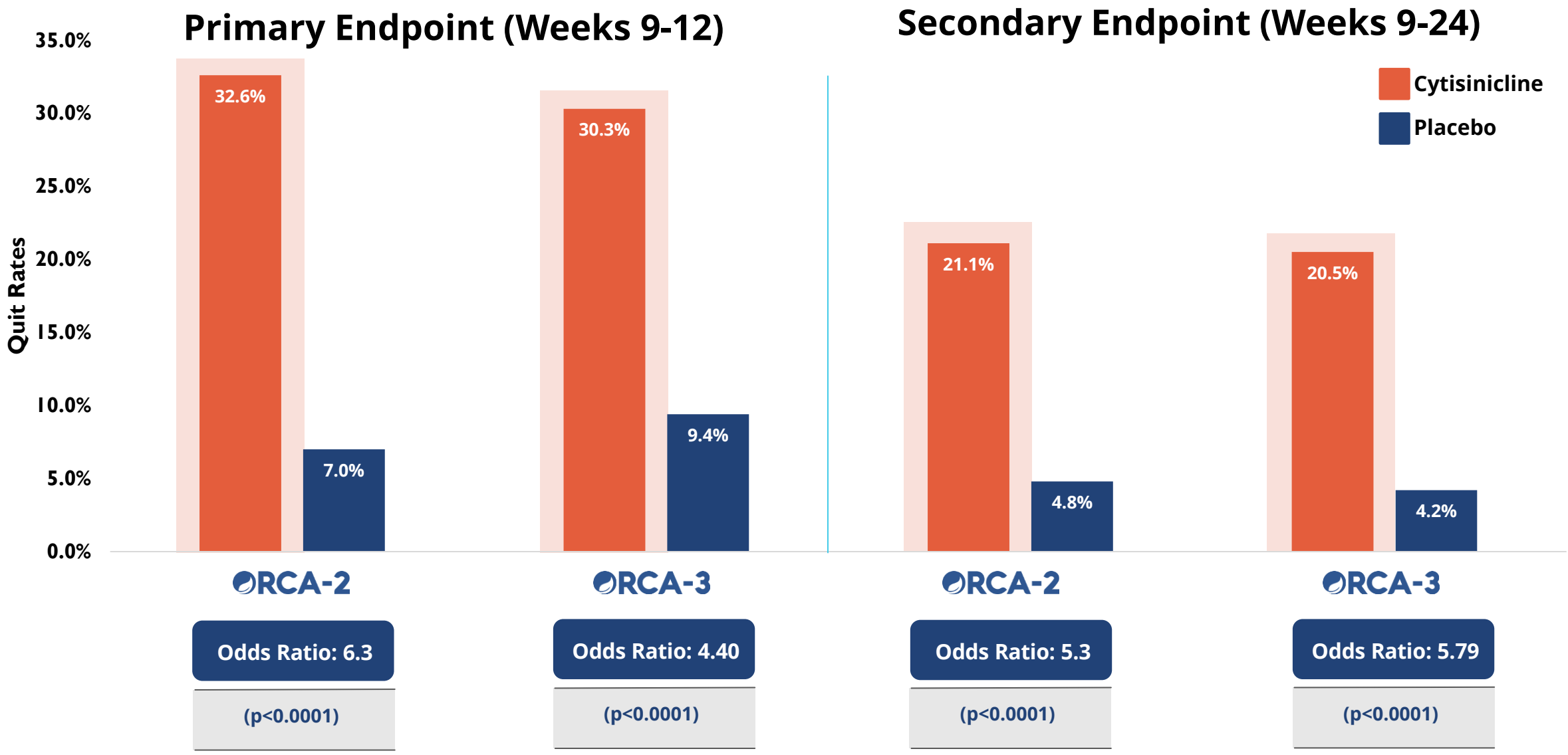
EDITORIAL

Cytisinicline to Speed Smoking Cessation in the United States

Jonathan Foulds, PhD; Sophia I. Allen, PhD; Jessica Yingst, DrPH

Phase 3 RCT Outcomes: ORCA-2 (N=810) and ORCA-3 (N=792)

Validated Continuous Abstinence: 12-week Cytisinicline vs. Placebo



- Questions and comments
- What other studies are needed?

Research Gaps: Scientific Questions to Consider

- **Effectiveness and safety in populations not included in RCTs**
  - Groups with high smoking prevalence or with less success with current treatments
  - Nonwhites, low-income populations, comorbid SUDS, mental health disorders, etc.
- **Effectiveness in actual medical practice**
  - Without intensive behavioral support
- **Effectiveness and safety compared to other cessation medications**
- **Effectiveness in combination with other cessation medications**
- **Effectiveness for nicotine dependence caused by other nicotine products**

Background: **Vaping Cessation**

- **Can cytisinicline treat other forms of nicotine addiction?**

- Some people who use nicotine e-cigarettes seek help to stop vaping.
- Little evidence exists to guide treatment, especially drug treatment.
  - Varenicline was effective in one RCT.*
  - USA: no medication is FDA-approved for vaping cessation.
  - UK: MHRA licensed a nicotine mouth spray that is approved for smoking cessation as a vaping cessation aid.

* Caponnetto P, et al. eClinicalMedicine, December 2023

Research Gaps: Efficacy for Vaping Cessation

JAMA Internal Medicine | Original Investigation

Online publication May 6, 2024

Cytisinicline for Vaping Cessation in Adults Using Nicotine E-Cigarettes
The ORCA-V1 Randomized Clinical Trial

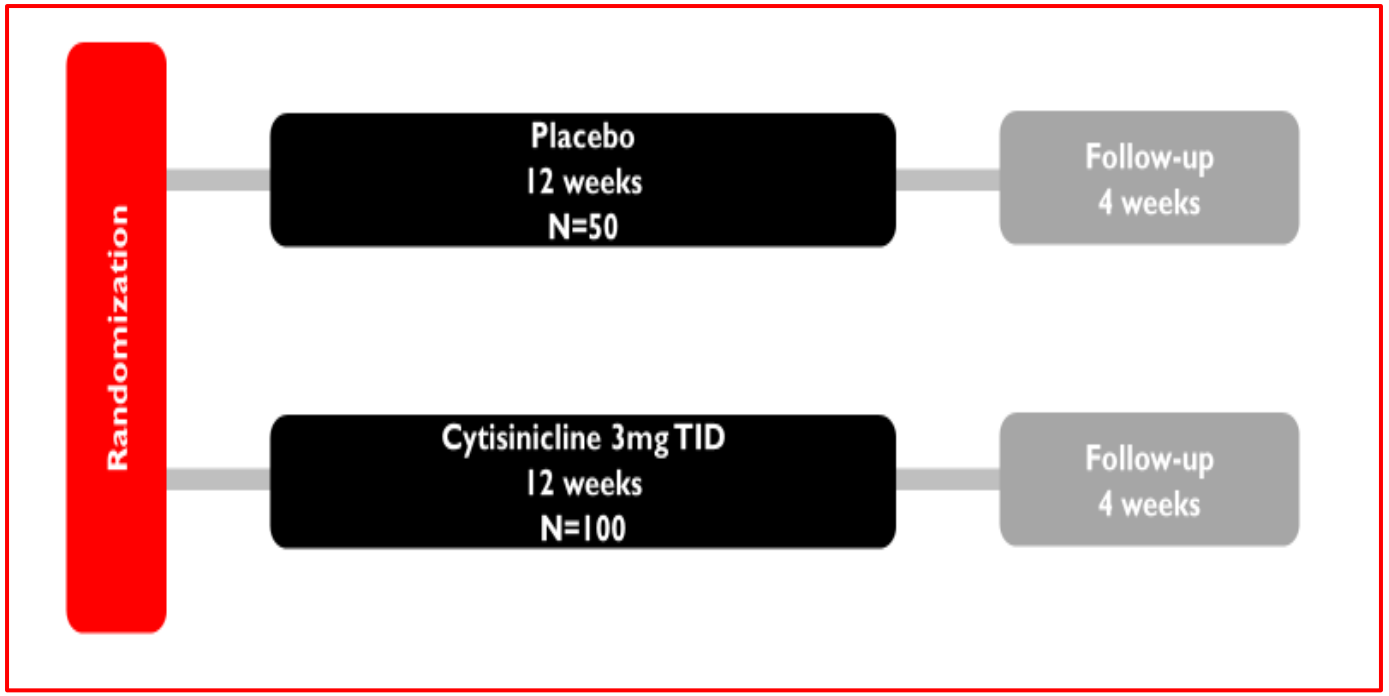
Nancy A. Rigotti, MD; Neal L. Benowitz, MD; Judith J. Prochaska, PhD, MPH; Daniel F. Cain, BSc; Julie Ball, MS; Anthony Clarke, PhD; Brent A. Blumenstein, PhD; Cindy Jacobs, PhD, MD

Funding: **National Institute of Drug Abuse** (#R44-DA054784) and Achieve Life Sciences

ORCA V1: Phase 2 Randomized Clinical Trial

- **AIM:** Compare the efficacy and safety of 12 weeks of the new cytisinicline regimen (3 mg TID) vs. placebo, both with behavioral support, for vaping cessation

- **STUDY DESIGN**
  - Double-blind RCT
  - Sample size goal: N=150
  - 2:1- cytisinicline: placebo
  - All take one pill TID x12 weeks
  - All: regular behavioral support
  - All followed for16 weeks



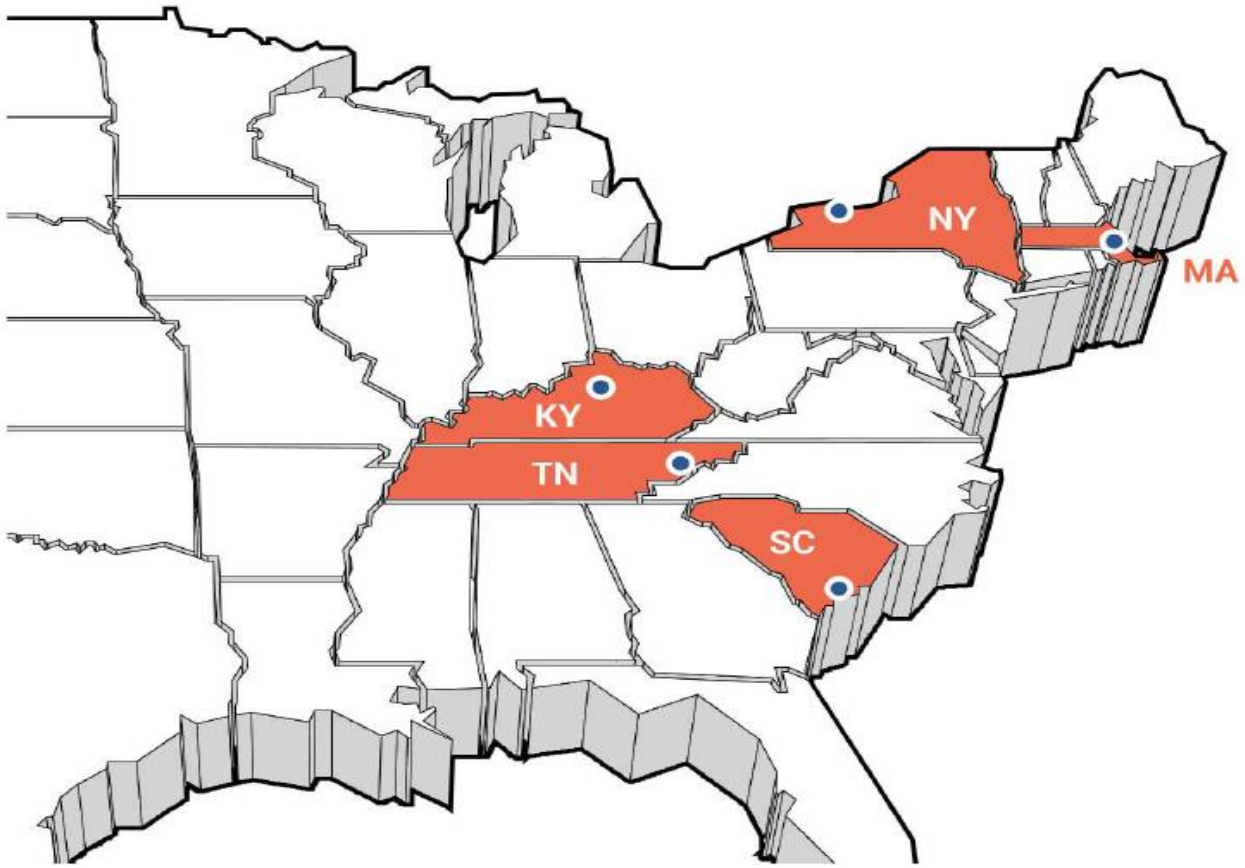
ORCA V1: Inclusion Criteria

- Age ≥18 years
- Daily use of a nicotine-containing e-cigarette (but no cigarette smoking)
  - Baseline saliva cotinine ≥30 ng/mL + expired air CO ≤ 9 ppm
- Seek to stop vaping
  - Agree to set quit date within 7-14 days of starting treatment
- Medically and psychiatrically stable *(similar criteria as ORCA-2)*
- Negative urinary screen for drugs of abuse *(cannabis allowed)*

Outcomes

- **Primary Outcome**
  - Biochemically verified continuous abstinence (cotinine <10 ng/mL) during the last 4 weeks of treatment (weeks 9-12)
- **Secondary Outcomes**
  - Continuous abstinence from last 4 weeks of treatment to 4 weeks post-treatment (weeks 9-16)
  - Past 7-day point prevalence e-cigarette vaping abstinence
- **Safety**
  - Adverse events, serious adverse events (#, severity, attributability to study drug)
- **Analysis**
  - Intent to treat. Assume that missing data = participant is vaping.

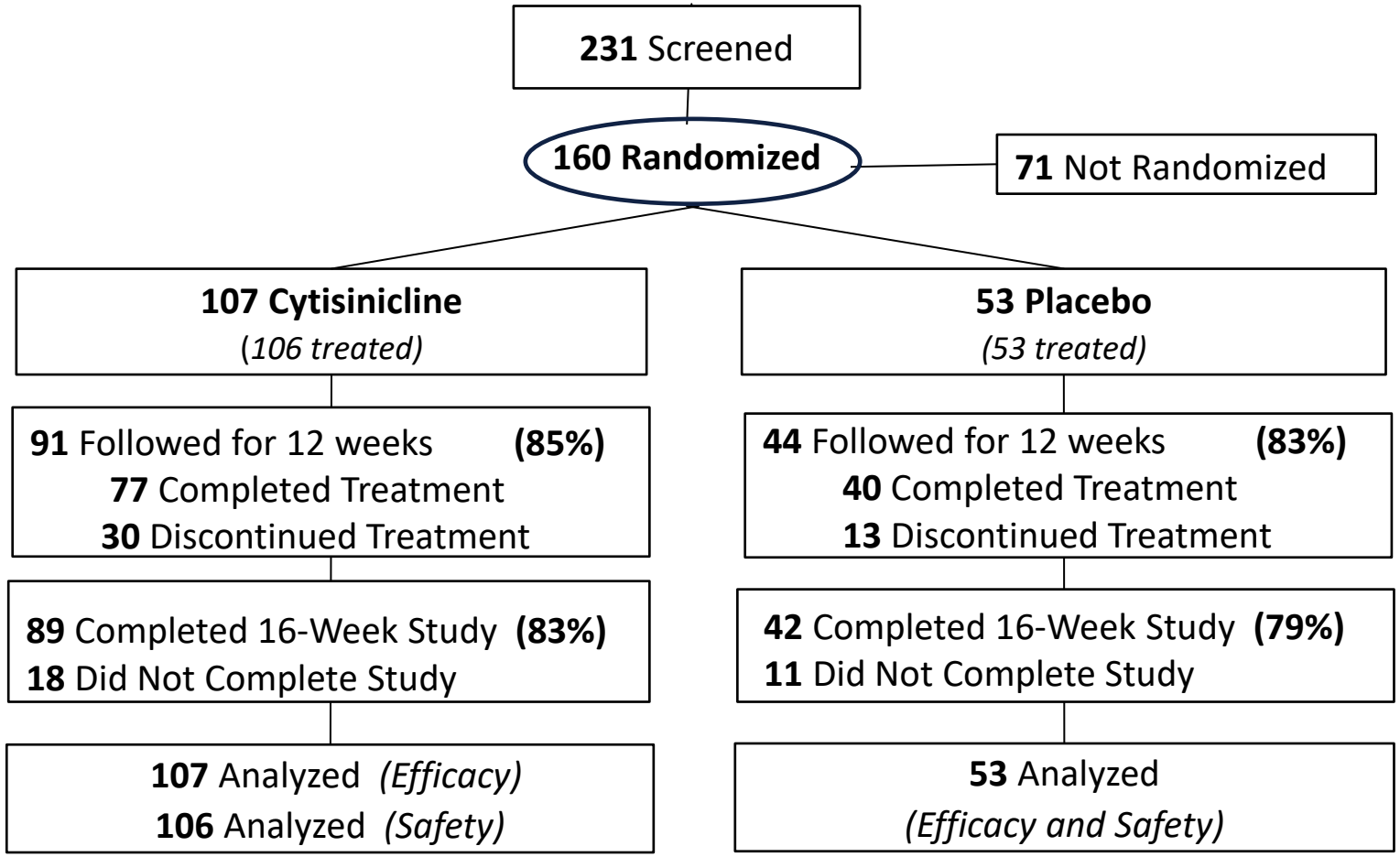
ORCA-V1: Participating Sites (N=5)



Enrollment
July – November 2022

Data collection ended
February 2023

ORCA-V1: CONSORT Diagram



160 randomized
(2:1 ratio)
Stratified by history of smoking

84% completed12 weeks

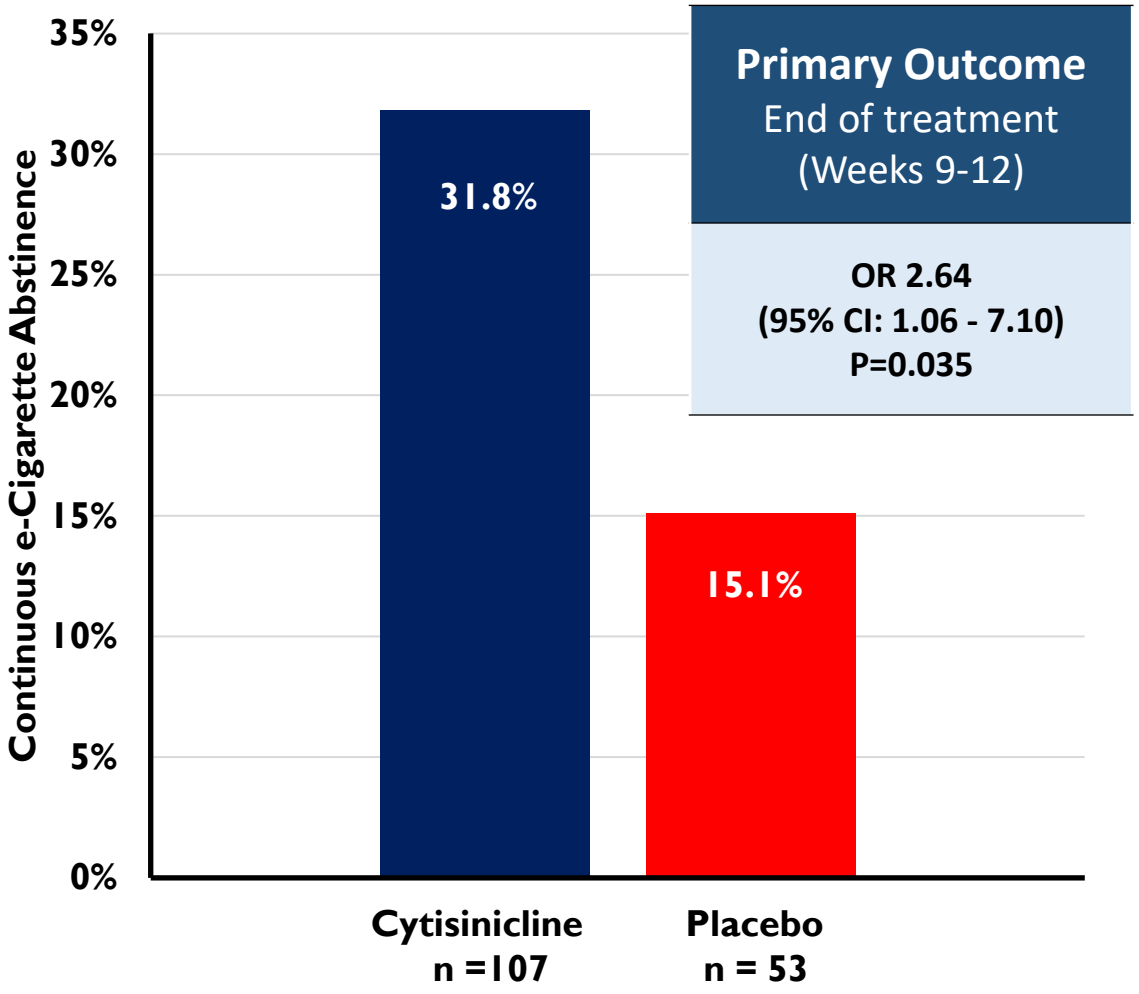
82% completed16 weeks

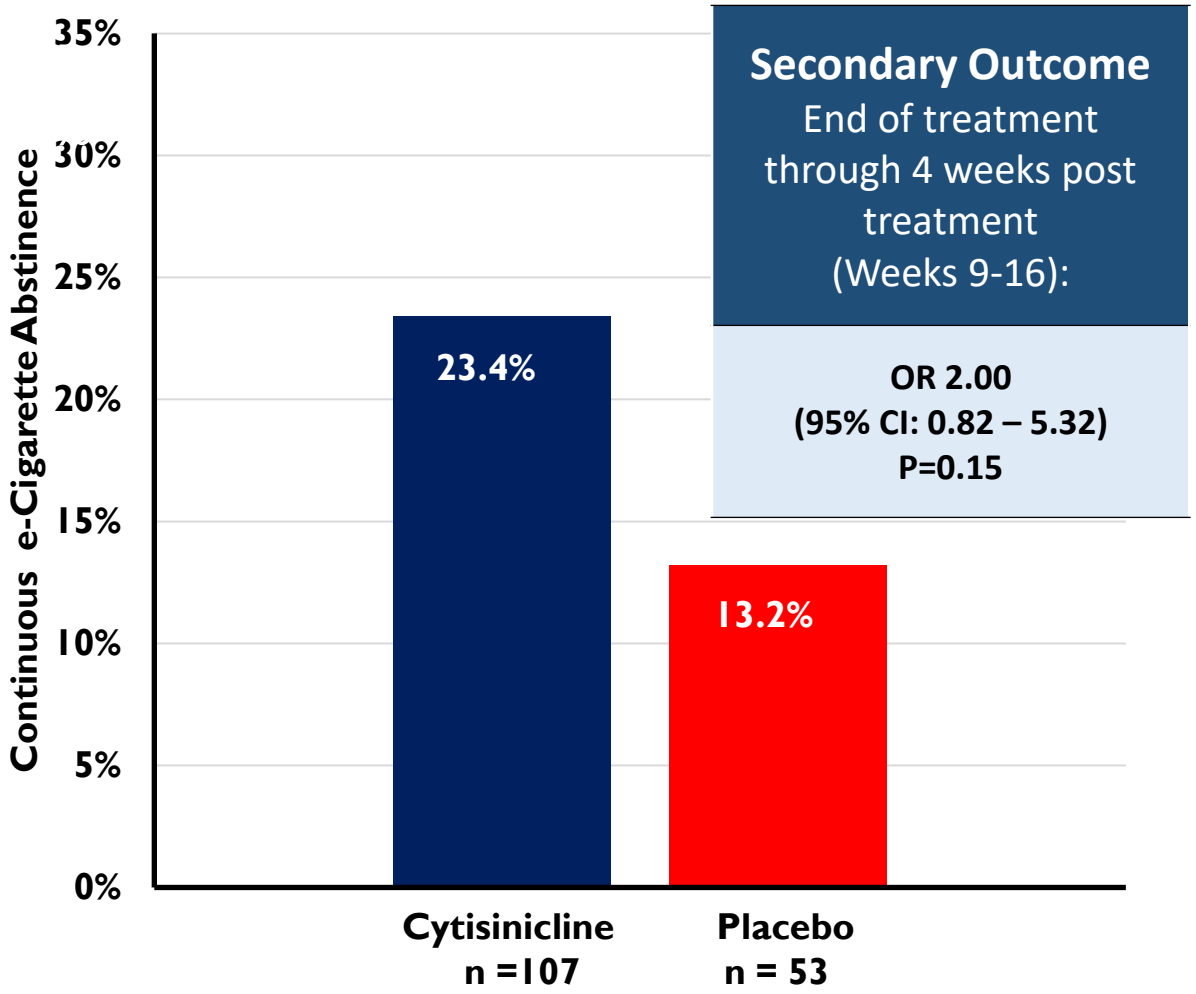
Intention-to-treat analysis

ORCA-V1: Study Participants, by Group

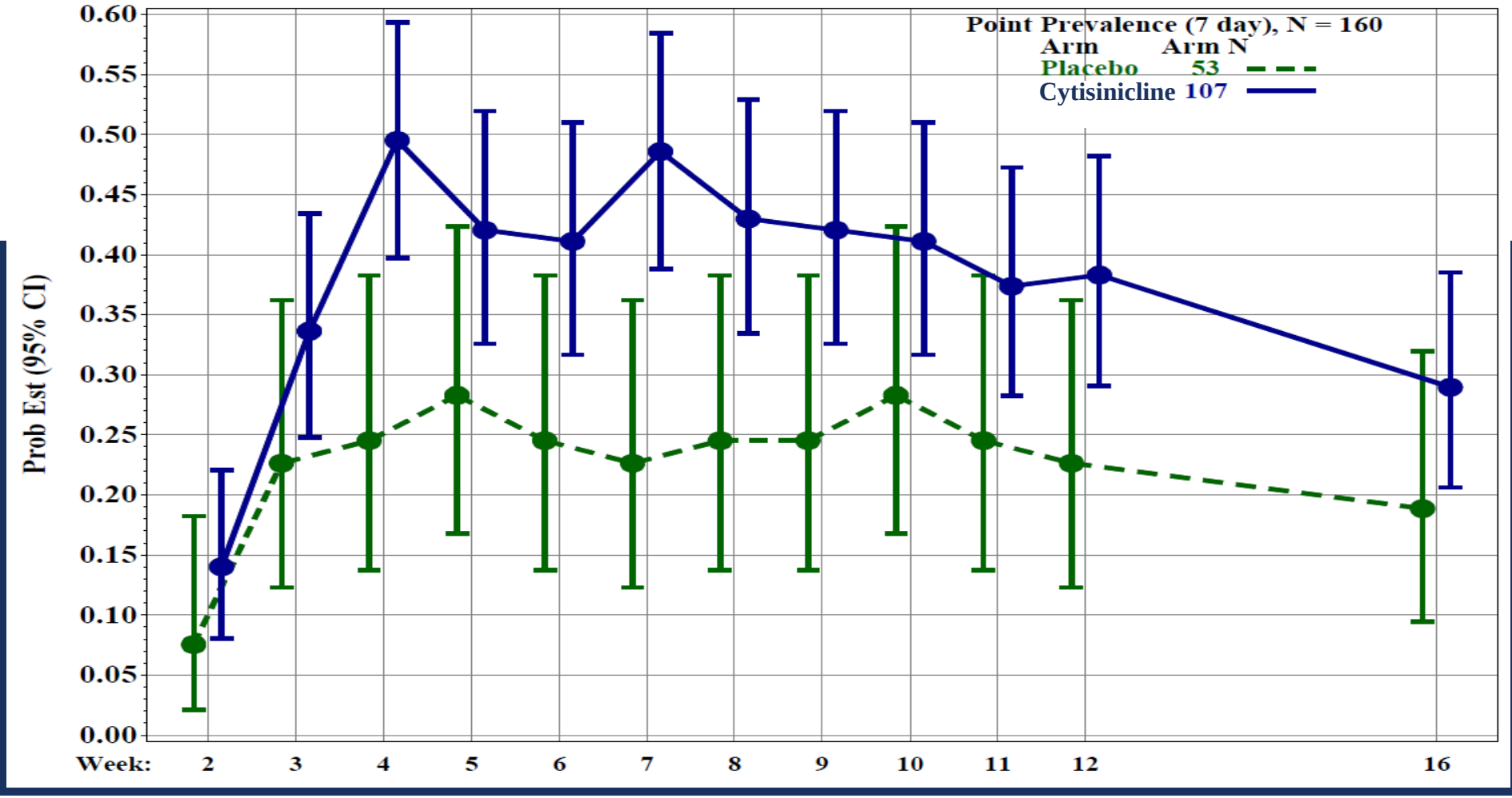
		Cytisinicline (N=107)		Placebo (N=53)	
Demographics		**n/mean**	**% / SD**	**n/mean**	**% / SD**
Age (mean years, SD)		**33.6**	11.2	**33.5**	10.9
Female sex – n (%)		54	**51%**	29	**55%**
Race – n (%)					
Black or African American		9	8%	5	9%
White		92	**86%**	43	**81%**
Other		6	6%	5	9%
Hispanic ethnicity-- n (%)		4	4%	5	9%
Cigarette smoking history (≥100 cigarettes) – n (%)		77	**72%**	38	**72%**
E-cigarette use					
Age at 1st e-cigarette use – median (range)		**27**	(12-58)	**24**	(16-60)
Device type	**Disposable**	38	**36%**	29	**55%**
	Pre-filled pod	33	31%	14	26%
	User-filled pod or tank	36	33%	10	19%
E-liquid Flavor	**Fruit**	61	57%	33	62%
	Menthol – mint	36	34%	17	32%
	Tobacco	11	**10%**	4	**8%**

Biochemically verified continuous abstinence





Point Prevalence E-cigarette Abstinence, by Group



ORCA-V1: Adverse Events by Treatment Group

Outcome Measure	Cytisinicline N=106		Placebo N=53	
	n	%	n	%
Participants with any serious adverse event	0	0%	0	0%
Participants with a treatment-emergent adverse event	54	50.9%	29	54.7%
Number of treatment emergent adverse events				
Mild	92	77.3%	38	55.9%
Moderate	26	21.8%	30	44.1%
Severe	1	0.9%	0	0%
Most common adverse events*				
Abnormal dreams	13	12.3%	1	1.9%
Insomnia	11	10.4%	1	1.9%
Nausea	5	4.7%	6	11.3%
Headache	7	6.6%	5	9.4%
Fatigue	6	5.7%	2	3.8%

** Excludes COVID infections or URIs*

ORCA-V1: Limitations

- Limited number of non-White or Hispanic participants.
- Excluded people with serious psychiatric illness and current illicit substance use.
- All received behavioral support for 12 weeks.
- Only adults were eligible. We cannot generalize to adolescent vapers.

ORCA-V1: Conclusions

- Cytisinicline 3 mg TID for 12 weeks, combined with behavioral support, is well tolerated and more effective than placebo to help e-cigarette users stop vaping at the end of the treatment period.
- Larger and longer duration trials are needed to confirm the effectiveness of cytisinicline at the end of treatment and determine if the benefit persists after treatment ends.
- Cytisinicline may offer adults an option to treat nicotine dependence due to e-cigarette use.

Cytisine: New Cochrane review (2023)

- Few RCTs met criteria to be included
- Cytisine is
  - More effective than placebo or no medication and well tolerated
    - RR 1.30 (95% CI: 1.15-1.47) 4 trials
  - More effective than NRT patch but only 1 trial (no meta-analysis)
    - RR 1.43 (95% CI: 1.13-1.80) 1 trial
  - May be comparable in effectiveness to varenicline with fewer side effects
    - RR 1.00 (95% CI: 0.79-1.26) 2 trials

Livingstone-Banks J et al. Nicotine receptor partial agonists for smoking cessation. Cochrane Database of Systematic Reviews 2023, Issue 6. Art. No.: CD006103.

Cytisine: Newer systematic review (May 2024)

- Done to support 1st WHO clinical treatment guideline for tobacco cessation in adults (July 3, 2024)
- Cytisine vs (placebo/usual care) RR 2.65 (95% CI: 1.50-4.67) 6 trials
- Cytisine vs. NRT: RR 1.36 (95% CI: 1.06-1.73) 2 trials
- Cytisine vs. varenicline RR 0.96 (95% CI: 0.63-1.45) 3 trials
- Conclusion: More effective than placebo, no medication, usual care, and NRT.

Puljevic C et al. Systematic review and meta-analysis of cytisine to support tobacco cessation. Addiction. 2024.

Next Steps for Cytisinicline – and some questions

- FDA has requested more data on safety with use up to 1 year
  - New non-randomized safety study started May 2024
- Achieve plans to submit New Drug Application to FDA in 1st half of 2025
- Cytisinicline might be approved for marketing in the U.S. as early as 2026
  - *Prescription only drug (Should it be OTC eventually?)*
  - *Brand name drug (Achieve has patents on 3 mg tablet and TID dosing)*
  - *What will the drug cost?*
  - *Will it reduce socioeconomic disparities in tobacco treatment access/success?*

Cytisine for Tobacco Cessation

Thank you

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