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Cytisinicline - Smoking Cessation
Virtual Roundtable

November 17, 2020

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 risk related to the impact on our business of the COVID-19 pandemic or similar public health crisis; 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.

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Introductions

Achieve Life Sciences

- John Bencich, Chief Executive Officer
- Cindy Jacobs, MD, PhD, President & Chief Medical Officer
- Anthony Clarke, PhD, Chief Scientific Officer

Smoking Cessation Expert Panel

- Nancy Rigotti, MD - Professor of Medicine, Harvard Medical School, Director of Tobacco Research & Treatment, Massachusetts General Hospital, and ORCA-2 Principal Investigator
- Mitchell Nides, PhD - President, LA Clinical Trials LLC, ORCA-1 Principal Investigator
- Neal Benowitz, MD - Professor of Medicine, Emeritus, University of California, San Francisco
- Judith Prochaska, PhD, MPH - Professor of Medicine, Stanford University
- Scott Leischow, PhD - Professor and Director, Clinical and Translational Science, Arizona State University, Former Senior Advisor for Tobacco Policy at HHS

Moderators

- Michael Higgins, Senior Equity Research, Ladenburg Thalmann
- Thomas Flaten, Senior Research Analyst, Lake Street Capital Markets

Agenda

- Welcome & Introductions (John Bencich)
- Presentation of ORCA-1 Trial Results (Dr. Nides)
- Recent Data from SRNT-E (Dr. Clarke)
- P3 Trial ORCA-2 Overview (Dr. Rigotti)
- Covid-19 & Smoking Cessation (Dr. Benowitz)
- Moderated KOL Roundtable Discussion
  - Michael Higgins, Ladenburg Thalmann and Thomas Flaten, Lake Street Capital Markets

Cytisinicline: A Potential New Treatment for Millions of Smokers

Achieve acquired the global rights to cytisinicline from Sopharma AD*

Exclusively focused on the development and commercialization of cytisinicline for smoking cessation & nicotine addiction

Robust Historical Data

- More than 10,000 participants in cytisinicline clinical trials to date
- Completed 3 investigator-led Phase 3 clinical trials in over 2,700 patients
- Over 20 years of in-market experience in over 20 million patients under brand name TABEX®
- Over 15 million cases in European safety database

Strong Execution

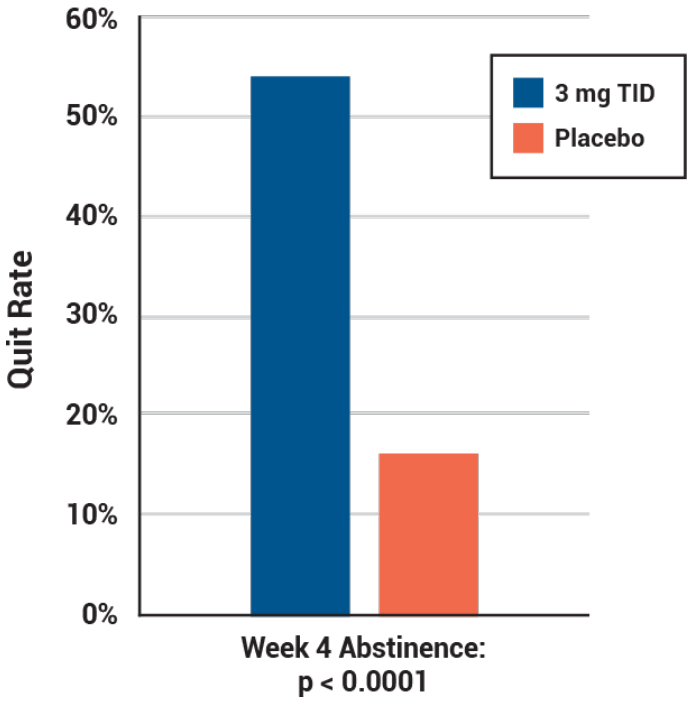
- NIH partnership to complete IND enabling studies
- Completed Phase 1/2 repeat-dose PK/PD study
- Phase 2b ORCA-1 trial completed in Q2 2019 showing statistically significant quit rates (N=254)
- Phase 3 ORCA-2 trial launched in Q4'20
- NDA plans already reviewed with FDA

* Excluding certain countries in Central and Eastern Europe, Scandinavia, North Africa, the Middle East and Central Asia, as well as Vietnam

Cytisinicline – Strong Value Proposition

Well-differentiated Product Profile	▪ Single & short course of treatment ▪ Dual-acting, highly selective MOA – improved tolerability ▪ Naturally-derived treatment
Solid Foundation of Clinical Evidence	▪ Favorable safety & efficacy from 3 prior Phase 3 trials in >2,700 patients ▪ More than 20M patients treated to date ▪ ORCA-1 study reinforces historical efficacy and safety data
Significant Market & Growth Potential	▪ 1.1B smokers worldwide[1] – more than 34M in U.S.[2] ▪ Smoking cessation market ~ $13B and growing[3] ▪ Most prescribed Rx (CHANTIX® - varenicline) sales of ~$1.1B in 2019[4] ▪ New treatment options required – nothing new in > 10 years
Addresses Global Public Health Epidemic	▪ Smoking and tobacco use is the leading cause of preventable death, responsible for ~7M lives lost annually worldwide[1] ▪ Nearly 30% of all cancer deaths in the U.S. are attributable to cigarette smoking[5]

Quit Rates for 3 mg TID vs Placebo



1. World Health Organization (WHO). WHO Report on the Global Tobacco Epidemic, 2017
2. Centers for Disease Control and Prevention (CDC). Tobacco Product Use Among Adults – United States, 2017
3. Coherent Market Insights, in its March 2017 report "Smoking Cessation and Nicotine De-addiction Products Market"
4. PFE Q4 & 2019 YE Results
5. American Cancer Society November 2015

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ORCA-1 Ongoing Research of Cytisinicline for Addiction

A multicenter, double-blind, randomized, placebo-controlled phase 2b trial of cytisinicline in adult smokers

Nides M.[1], Rigotti N.[2], Benowitz N.[3], Cain D.[4], Clarke A.[4], Jacobs C.[4]

[1] Los Angeles Clinical Trials, Burbank, United States
[2] Massachusetts General Hospital/Harvard Medical School, Boston, United States
[3] University of California San Francisco, San Francisco, United States
[4] Achieve Life Sciences, Inc., Seattle, United States

ORCA-1 Phase 2b Dose Selection Study (N=254)

Objective:

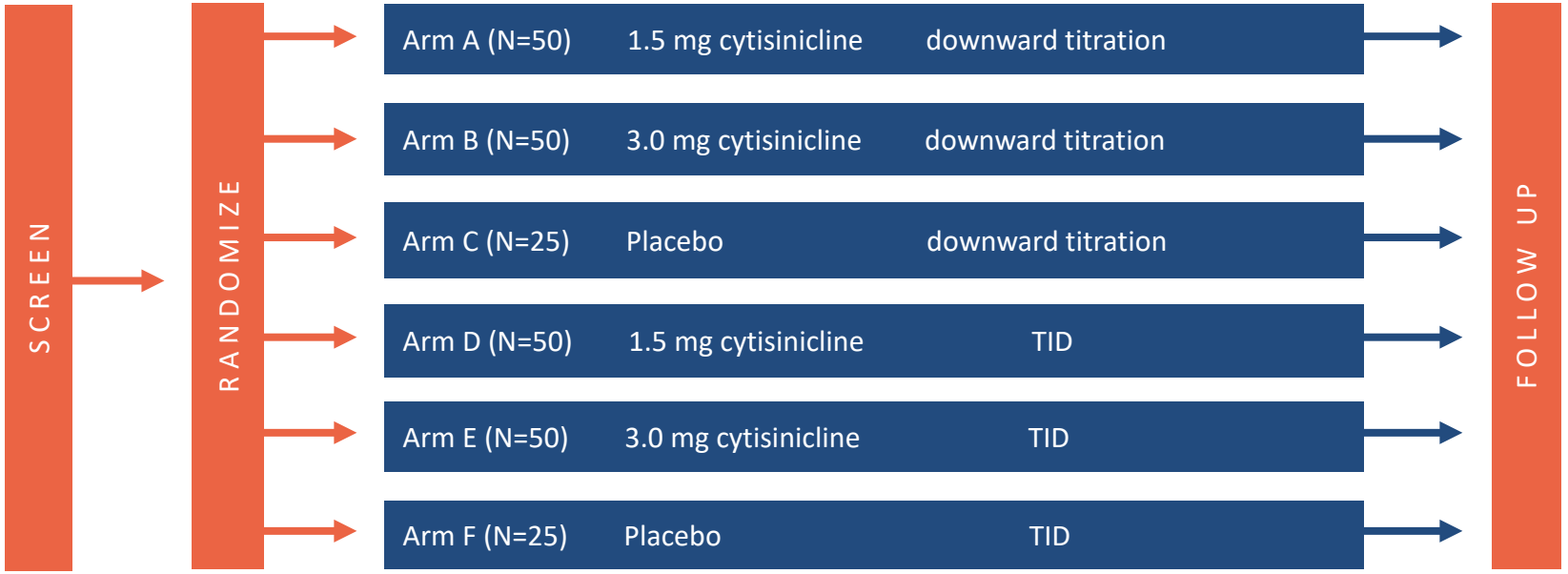
- To optimize Phase 3 trial planning for dosing, scheduling, compliance and efficacy rates in U.S.
- Evaluate safety and efficacy of 1.5mg and 3mg of cytisinicline vs placebo administered over 25 days
- All subjects to receive standardized behavioral support and will be followed up out to 8 weeks

Population:

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

Endpoints:

- Biochemically verified abstinence
- Reduction in self reported cigarettes smoked during treatment

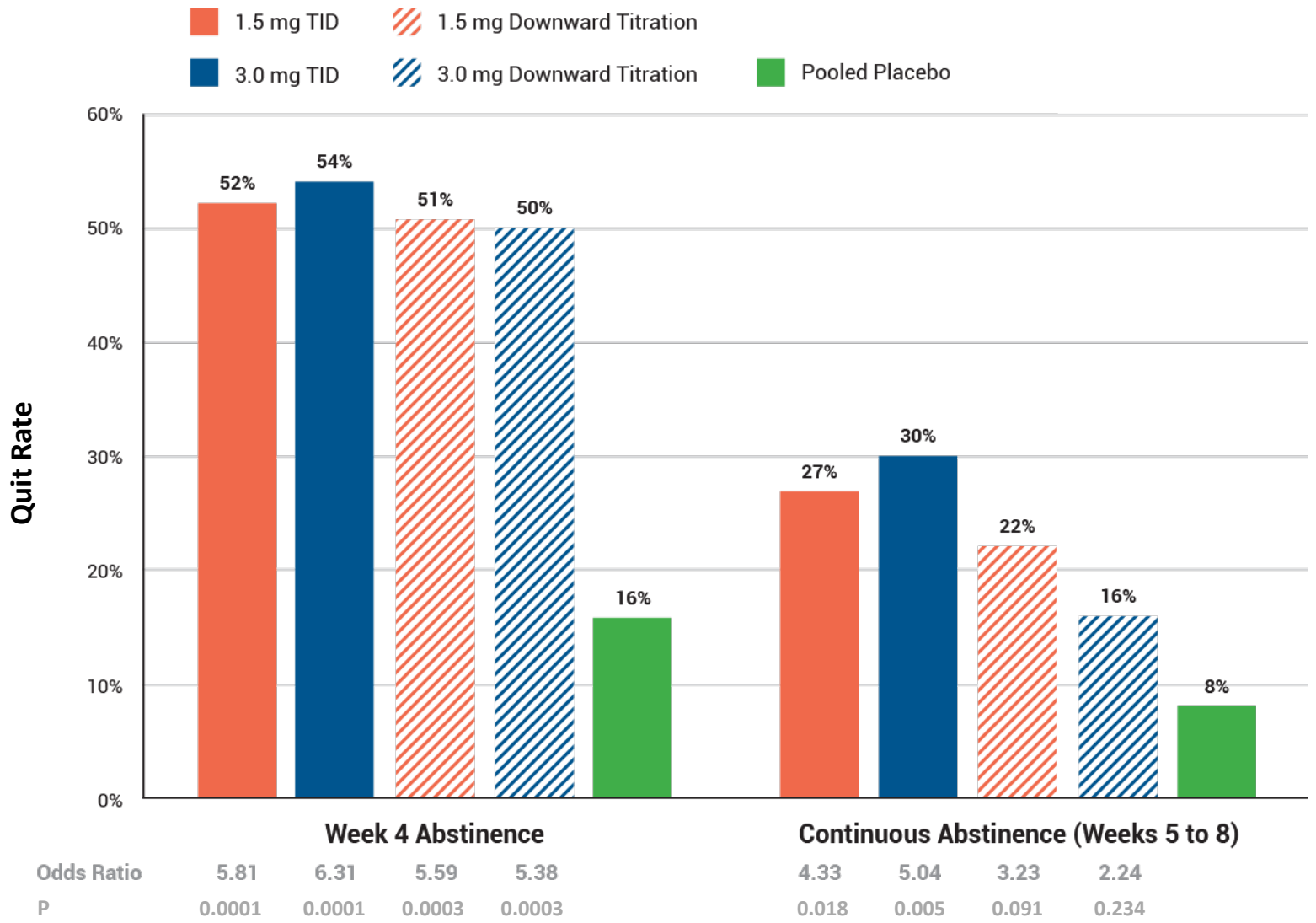


ORCA Ongoing Research of Cytisinicline for Addiction

ORCA-1 Dose Selection Study Results: Baseline Subject Demographics

	TID		Downward Titration			
	1.5 mg (n=52)	3.0 mg (n=50)	1.5 mg (n=51)	3.0 mg (n=50)	Pooled Placebo (n=51)	ALL (n=254)
Smoking duration (mean years)	30.9	30.0	33.3	33.2	33.0	32.1
Daily smoking (median cigarettes)	20	18	20	20	20	20
Prev. quit attempts (mean)	4.7	3.8	5.4	3.8	4.9	4.5
Previous treatments						
Varenicline	21 (40%)	18 (36%)	21 (41%)	13 (26%)	19 (37%)	92 (35%)
Bupropion	9 (17%)	7 (14%)	9 (18%)	3 (6%)	12 (24%)	40 (16%)
NRT	27 (52%)	25 (50%)	23 (45%)	19 (38%)	28 (55%)	122 (48%)
Patch	22 (42%)	16 (32%)	21 (41%)	12 (24%)	26 (51%)	97 (38%)
All other NRT						
e-cigarettes	19 (37%)	13 (26%)	15 (29%)	11 (22%)	18 (35%)	76 (30%)

ORCA-1 Dose Selection Study Results: Significant Increase in Quit Rates Across All Cytisinicline Arms



- All cytisinicline arms demonstrated statistically significant end of treatment quit rates (>= 50%; p<0.001)
- TID administration outperformed the downward titration groups at both end of treatment and weeks 5-8
- 3.0 mg dose with TID administration selected to move forward to Phase 3 development

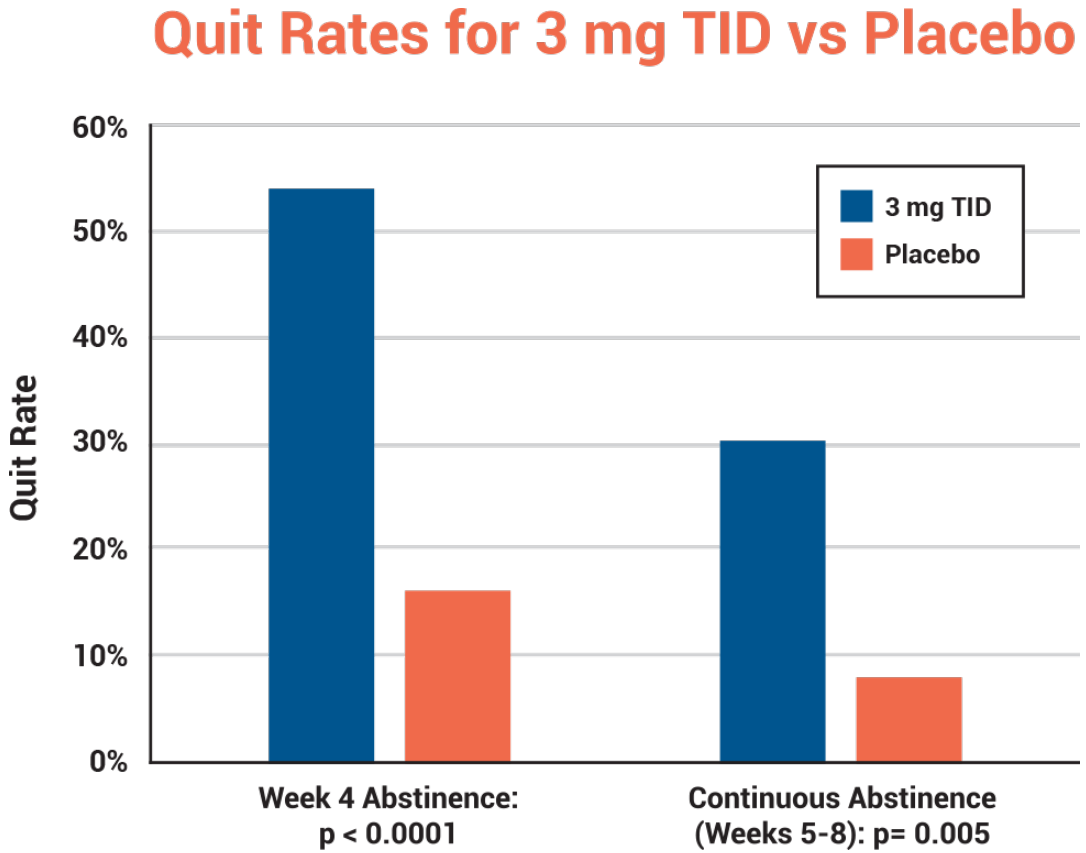
ORCA-1 Dose Selection Study Results: Confirmation of Safety & Tolerability

Most commonly reported (>5%) side effects from ORCA-1:

Adverse Event	3.0 mg TID (n=50)	Pooled Cytisinicline (n=203)	Placebo (n=51)
At least 1 AE	42%	46%	47%
Upper Respiratory Tract Infections	6%	6%	14%
Nausea	6%	6%	10%
Abnormal Dreams	6%	9%	2%
Insomnia	6%	7%	2%
Constipation	6%	2%	2%
Headache	4%	5%	4%

- Cytisinicline was generally well-tolerated across all treatment groups
- Overall low incidence of adverse events
- No serious or severe adverse events reported
- Low rates of AE's compares favourably to currently approved smoking cessation products

ORCA-1 Dose Selection Study Results: Statistically Significant Efficacy Observed for 3.0 mg TID



Characteristic	3.0 mg CYT (N=50)	Placebo (N=51)	P Value
Reduction in expired CO[1]	80%	38%	p = 0.003
4 Week Abstinence [2]	54%	16%	p < 0.001
Continuous Abstinence (Weeks 5-8)[3]	30%	8%	p = 0.005

- Statistically significant quit rates demonstrated at both end of treatment and weeks 5 through 8 (the FDA approvable endpoint)
- CO confirmed end of treatment quit rates on Cytisinicline exceeded Chantix, Zyban & NRT quit rates at both week 4 and week 12 (end of treatment) in latest EAGLES study[4]
- Adherence to study treatment was 98% in the 3.0 mg TID arm
- Cytisinicline was generally well-tolerated with no serious adverse events reported
- 3.0 mg dose with TID administration selected to move forward to Phase 3 development

1. Average % reduction expired CO from Baseline by Day 26
2. Biochemically confirmed quit on Day 26 (no cigarettes smoked and expired CO<10 ppm)
3. Biochemically confirmed on Day 26 and weeks 5, 6, 7, & 8 (no cigarettes smoked and expired CO<10 ppm)
4. EAGLES: Anthenelli et al; Lancet; 2507-20, June 18, 2016

RAUORA

Nau te kakahu i whatu.
He taniko taku.

RAUORA Trial of Cytisinicline vs Varenicline in the Māori of New Zealand

Dr. Anthony Clarke

Chief Scientific Officer, Achieve

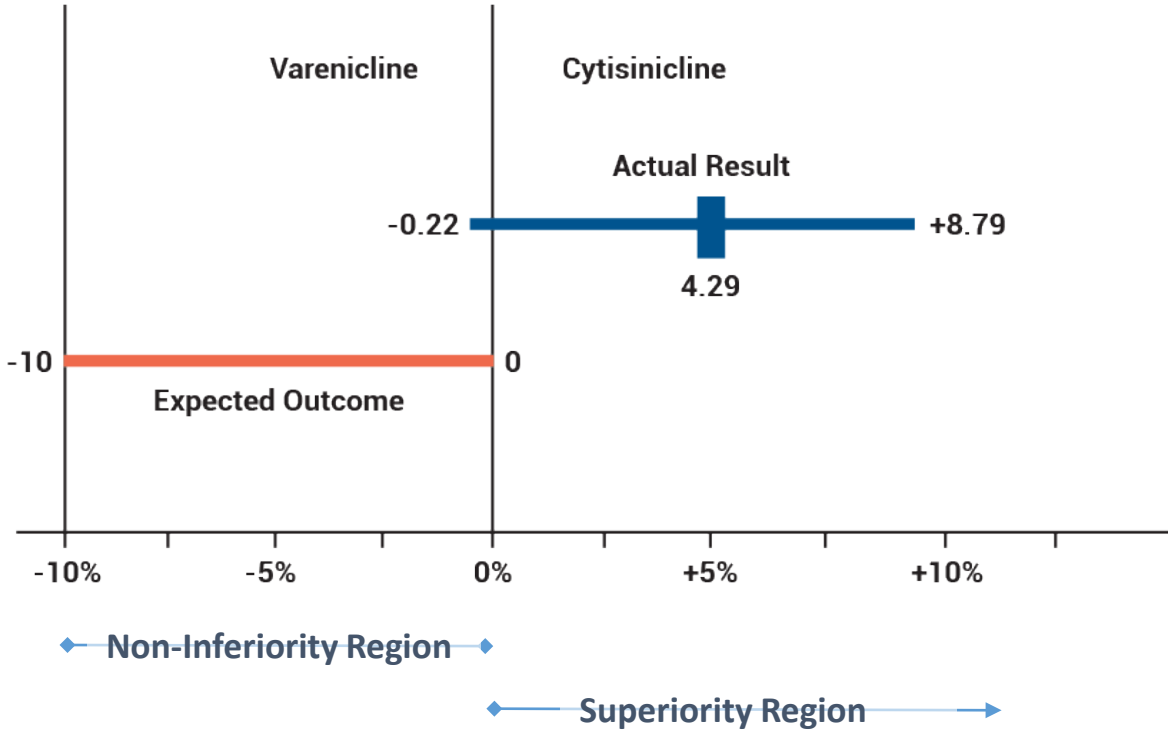
RAUORA Study Design

- Direct comparison of the efficacy and safety of cytisinicline and varenicline in Māori of New Zealand
- Enrolled 679 daily smokers from a target sample size of 2,140
- Non-inferiority design with the following prior assumptions
  - Varenicline is the gold standard: Cytisinicline will be inferior in efficacy
  - Non-inferiority margin is 10%
    (i.e. cytisinicline will be declared as non-inferior to varenicline if the efficacy difference is less than 10%)
- Treatment for 12 weeks
  - Varenicline duration according to PI
  - Cytisinicline 1.5 mg according to European PI to day 24, then 1.5 mg twice daily maintenance dose
- Primary outcome
  - Biochemically-verified smoking cessation after 6 months

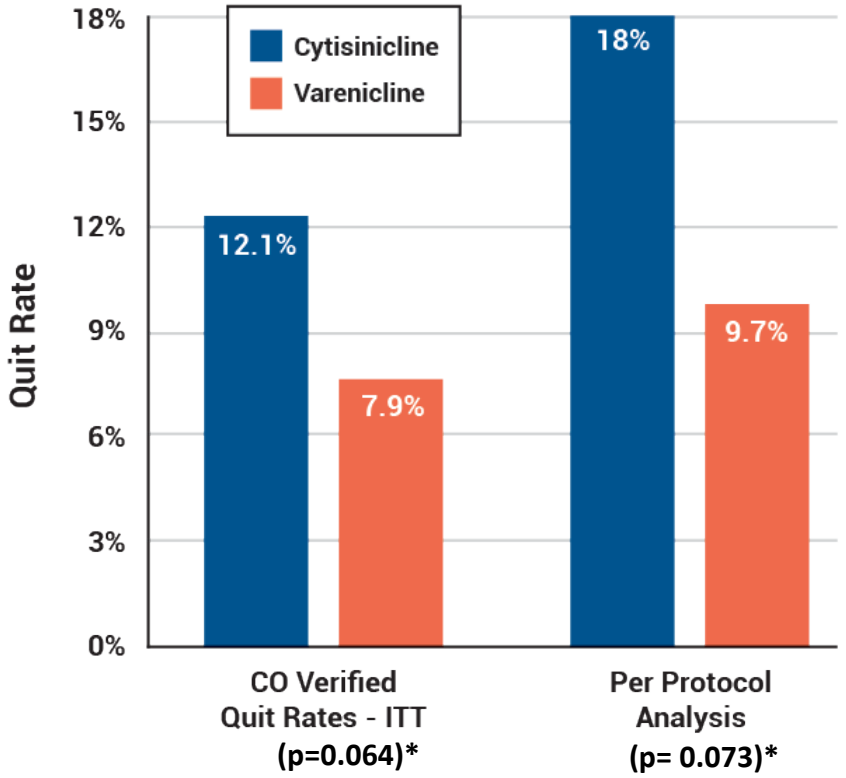
Nau te kakahu i whatu.
He taniko taku.

6 Month Quit Rates Trended Towards Superiority for Cytisinicline

Risk Difference at 6 Months



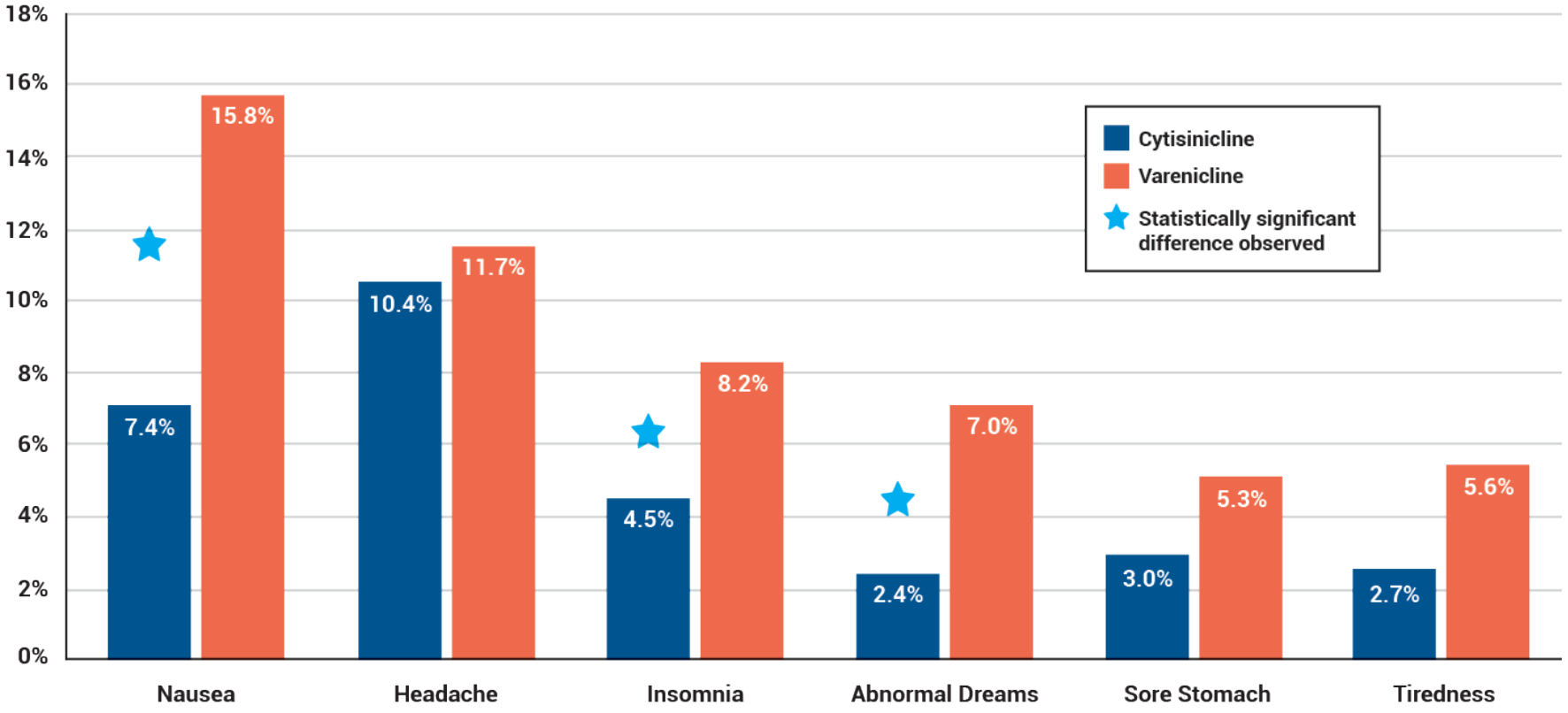
6 Month Quit Rate



*P values calculated based on chi-square analysis of quit rates

Significantly Fewer Overall Adverse Events (p<0.001)

Adverse Events (>5% of Subjects)



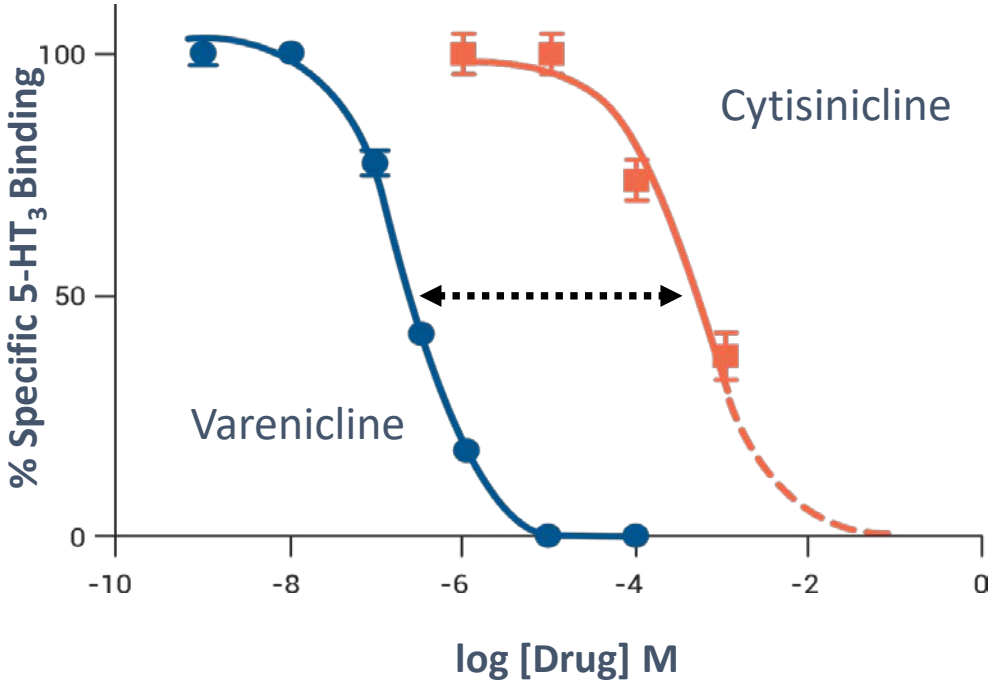
- **Cytisinicline had overall significantly fewer adverse events than varenicline (p<0.001)**
- Varenicline showed significantly increased nausea, abnormal dreams & insomnia (p<0.05)

Achieve analysis of adverse event data based on Mantel-Haenszel chi-square test comparing rates in the cytisinicline and varenicline arms (# subject affected/#subjects exposed)

Nau te kakahu i whatu.
He taniko taku.

Chantix Adverse Events Likely Due to Off Target Activity

	Ki (nM)		
	Varenicline	Cytisinicline	Ratio
α4β2	0.06	0.17	2.8
α3β4	240	840	3.5
α7	322	2,400	7.5
5-HT$_3$	83	170,000	**2,048**



- 5-HT$_3$ receptor activation causes nausea and vomiting
- Cytisinicline is over 2000-fold less potent than varenicline at the human 5-HT$_3$ receptor
- Differences in the incidence of nausea and vomiting for varenicline and cytisinicline are predicted from differences in human 5-HT$_3$ receptor agonist activity

ORCA-2 Ongoing Research of Cytisinicline for Addiction

Phase 3 ORCA-2 Trial of Cytisinicline in Adult U.S. Smokers

Nancy Rigotti, MD

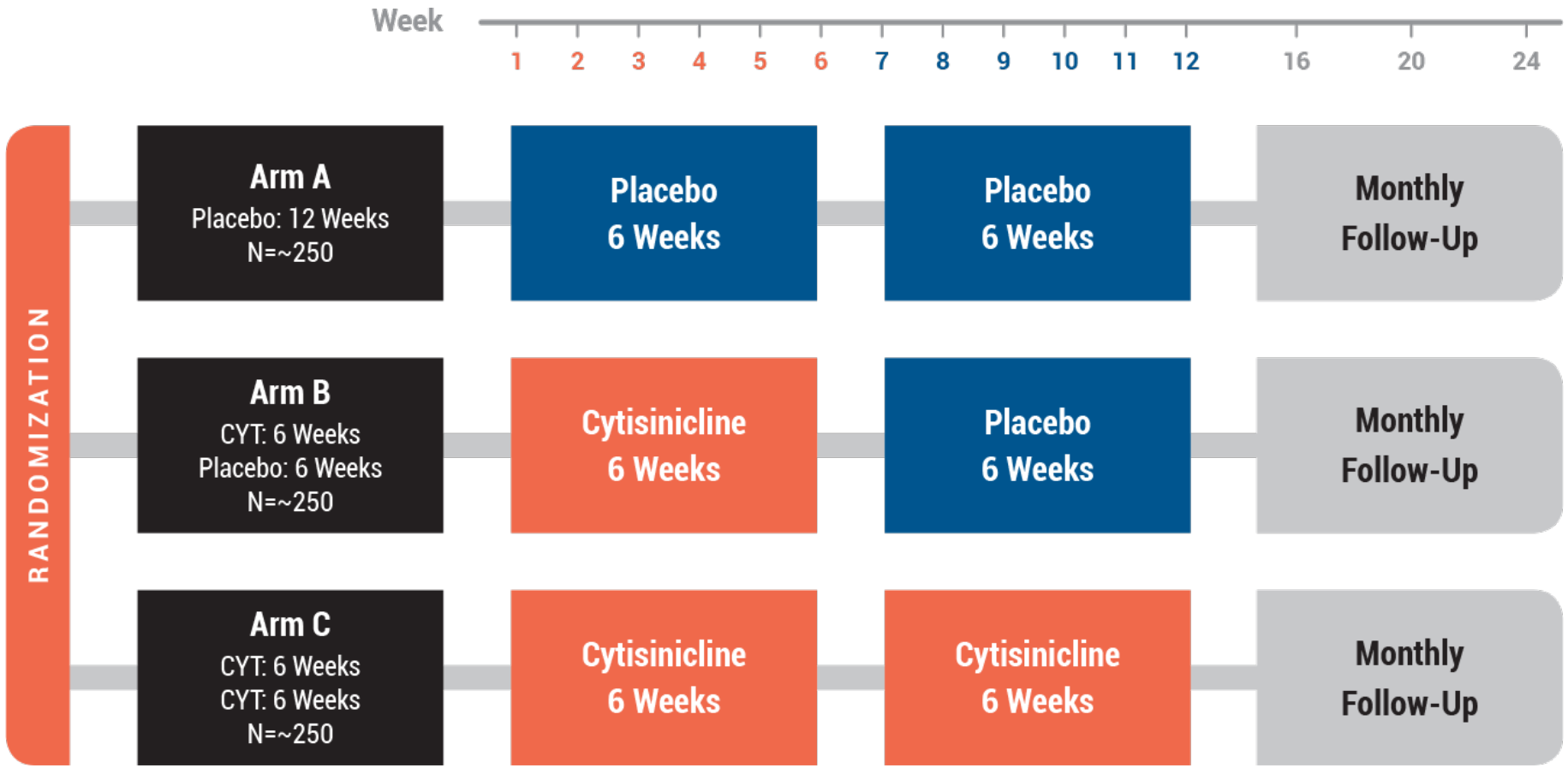
Professor of Medicine, Harvard Medical School

Associate Chief, Division of General Internal Medicine

Director, Tobacco Research and Treatment Center

Massachusetts General Hospital

Overview of ORCA-2 Phase 3 Study Design



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

Study Population: 750 Smokers of ≥10 cigarettes/day and expired air CO > 10 ppm

ORCA-2: Study Population

Main Inclusion Criteria

- Current daily cigarette smokers: average of 10 or more cigarettes/day AND expired air CO ≥10 ppm
- Intend to quit smoking now
- Failed at least 1 previous attempt to stop smoking with or without therapeutic support
- Willing to participate in the smoking cessation behavioral support provided throughout the study

Main Exclusion Criteria

- Current or planned use of other smoking cessation medications during the study
- Clinically abnormal laboratory values
- Uncontrolled hypertension, abnormal ECG, or recent acute myocardial infarction, stroke, or heart failure admission
- Psychiatric: (1) schizophrenia or bipolar disorder, (2) current moderate to severe depression symptoms, (3) high risk of suicide ideation
- Pregnant or breast-feeding women or unwilling to use acceptable methods of birth control during the study

ORCA-2: Multiple Primary & Secondary Endpoints

Two Primary Endpoints for biochemically verified continuous abstinence during the last 4 weeks of treatment

- Arm B vs Arm A: Smoking abstinence during weeks 3-6
- Arm C vs Arm A: Smoking abstinence during weeks 9-12

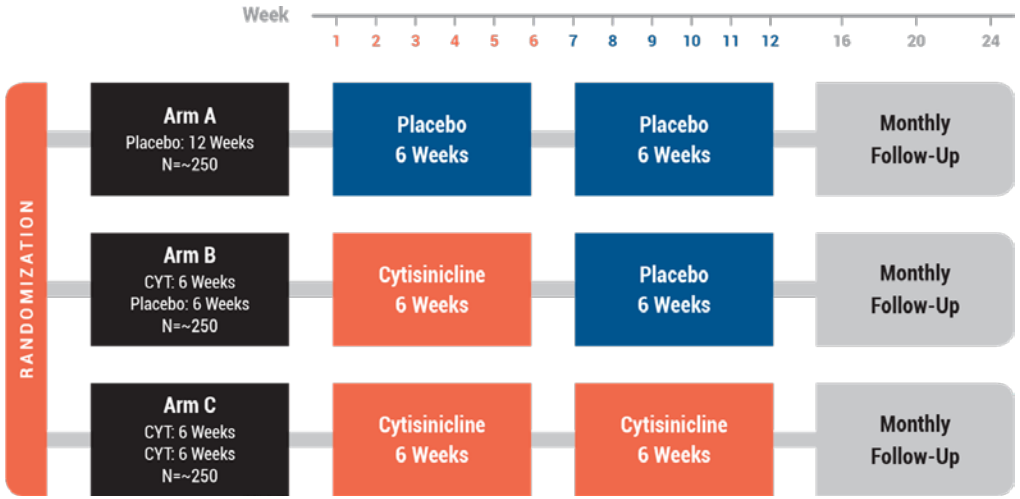
Three Secondary Endpoints:

Two secondary endpoints evaluate for biochemically verified continuous abstinence through Week 24

- Arm B vs Arm A: Smoking abstinence from Week 6 to 24 weeks
- Arm C vs Arm A: Smoking abstinence from Week 12 to 24 weeks

Third secondary endpoint evaluates reduction in risk of relapse

- Arm C vs Arm B: Reduction in risk of relapse at Week 24 comparing subjects receiving 12 weeks cytisinicline to receiving 6 weeks cytisinicline



Overall Type I error probability specified to be one-sided 0.025 (using Hochberg method for multiple endpoints)

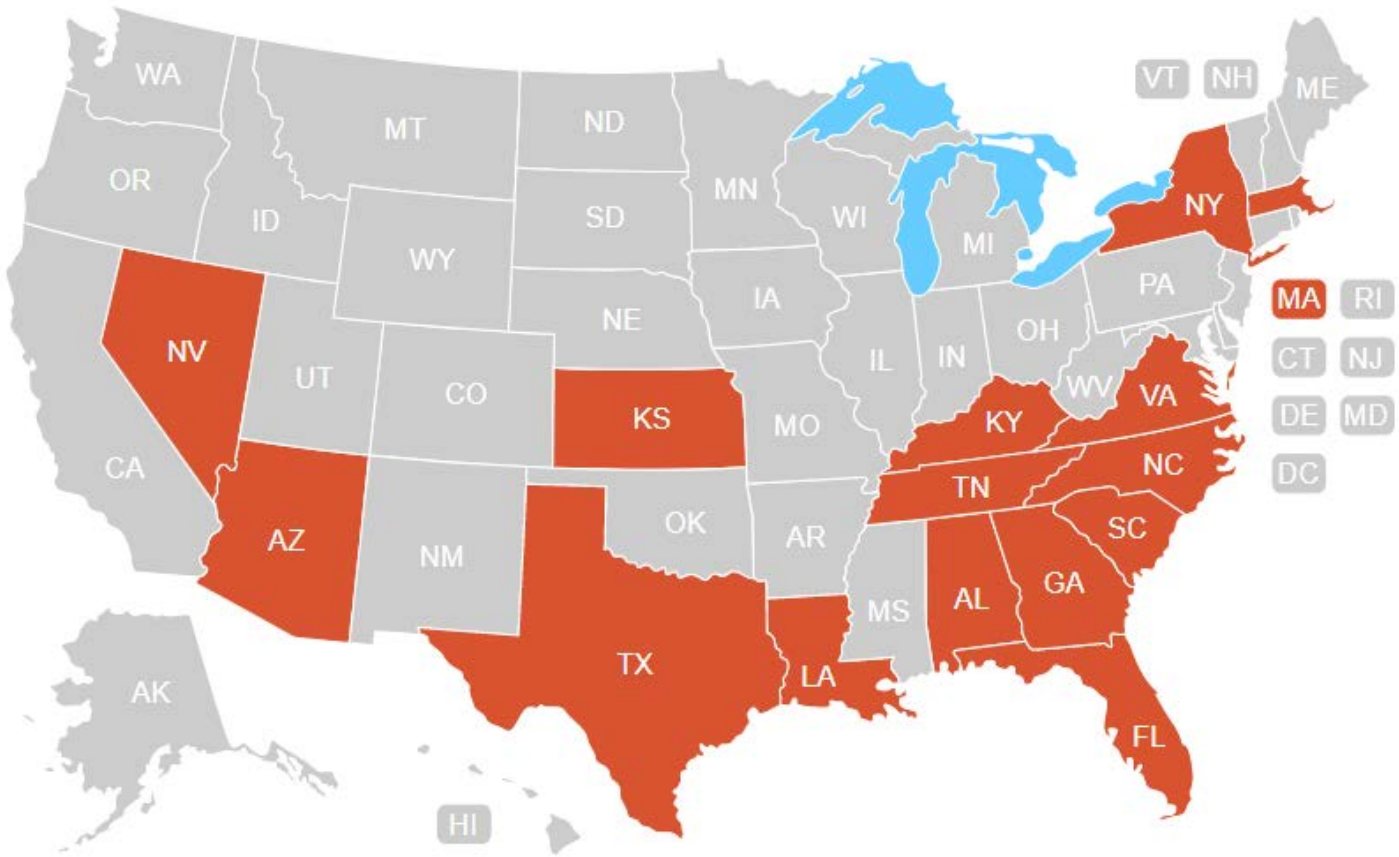
Study size and specifications at ~95% power for the 24-week comparisons with critical odds ratio of ≥1.83 for significance.

Current Status of ORCA-2 Phase 3 Study

- Study design incorporates prior FDA recommendations
  - Higher (3mg) cytisinicline dose
  - Simplified treatment schedule (TID)
  - Slightly longer overall treatment (6 weeks instead of 25 days) and 12 weeks of treatment for higher abstinence rates and/or possible reduction in relapse
- Meeting with FDA in November 2019: Reached agreement on study design, endpoints and primary/secondary analyses
- COVID-19 pandemic delayed study initiation
- FDA reviewed final protocol in September 2020
  - Minor recommendations to add one nicotine withdrawal evaluation and one more exploratory study evaluation
- Phase 3 ORCA-2 Study initiated screening in October 2020
  - 15 sites now active and enrolling subjects

ORCA-2 Phase 3: Participating Sites (N=15)

ORCA-2 Site Locations
Lexington, Kentucky
Knoxville, Tennessee
Mt. Pleasant, South Carolina
Rochester, New York
Phoenix, Arizona
Boston, Massachusetts
Dallas, Texas
Mobile, Alabama
Atlanta, Georgia
Wichita, Kansas
Raleigh, North Carolina
Las Vegas, Nevada
Norfolk, Virginia
New Orleans, Louisiana
Coral Gables, Florida



https://clinicaltrials.gov/ct2/show/NCT04576949?term=cytisinicline&draw=2&rank=1

COVID-19 Risk Mitigation

COVID-19 Mitigation Plans for ORCA-2 Study

- Only 1 study site in each state
- 13/15 sites are designated as essential businesses and stayed open throughout 2020 conducting other trials
- All sites have procedures in place to handle potential increase in COVID-19 cases and to handle COVID-19 + subjects
- All sites have additional contingency plans to cover possibility of site closure, subject(s) and/or staff becoming COVID+. Focus is on minimizing any possible data loss (e.g. home evaluations or virtual monitoring)
- Achieve Project Director meets weekly with senior clinical site management team representing 9 of the participating sites
- Plan to discuss any issues of missing data with FDA prior to final study analyses

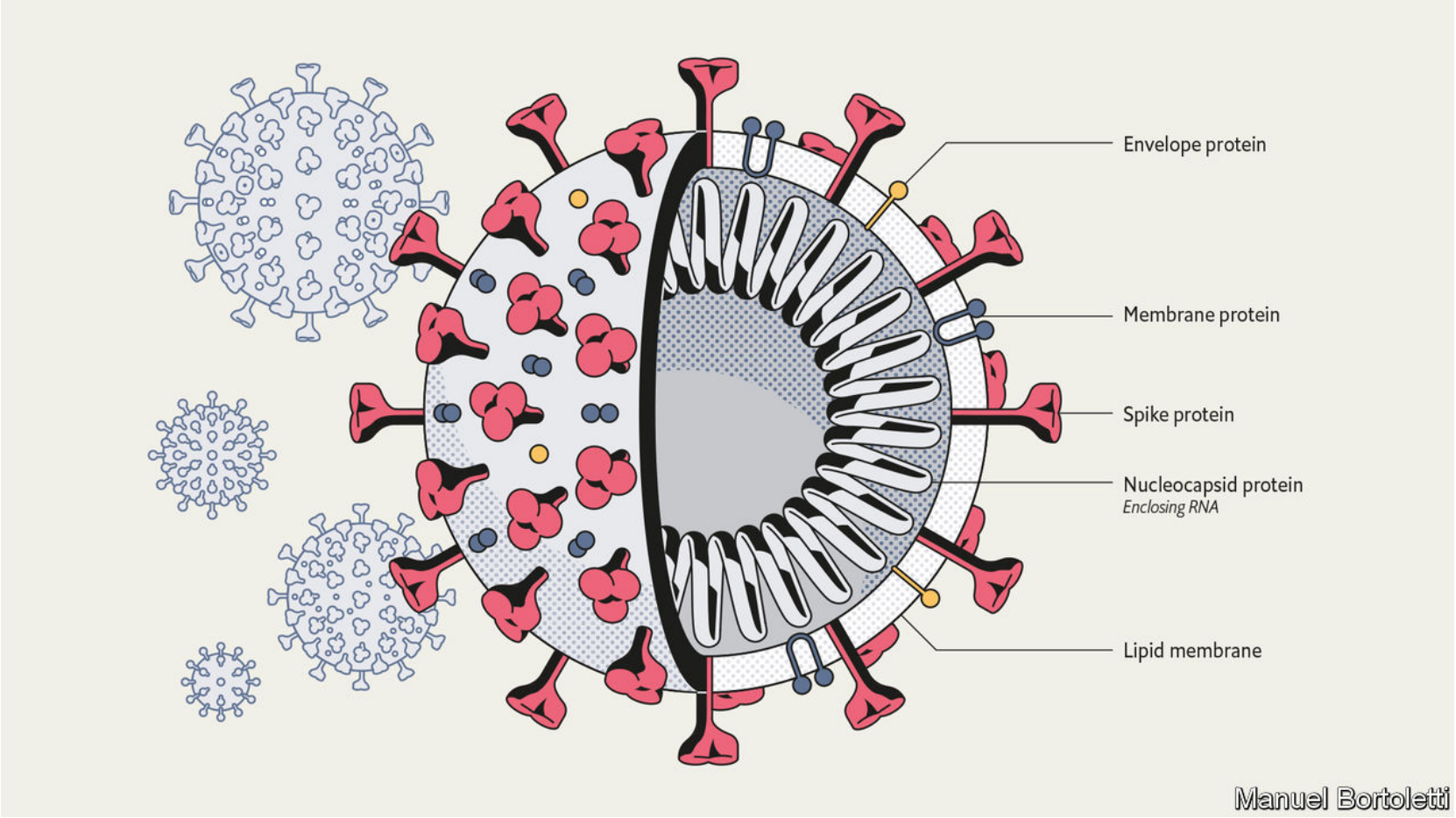
Cigarette Smoking and COVID-19 Infection

Neal L Benowitz MD
University of California
San Francisco

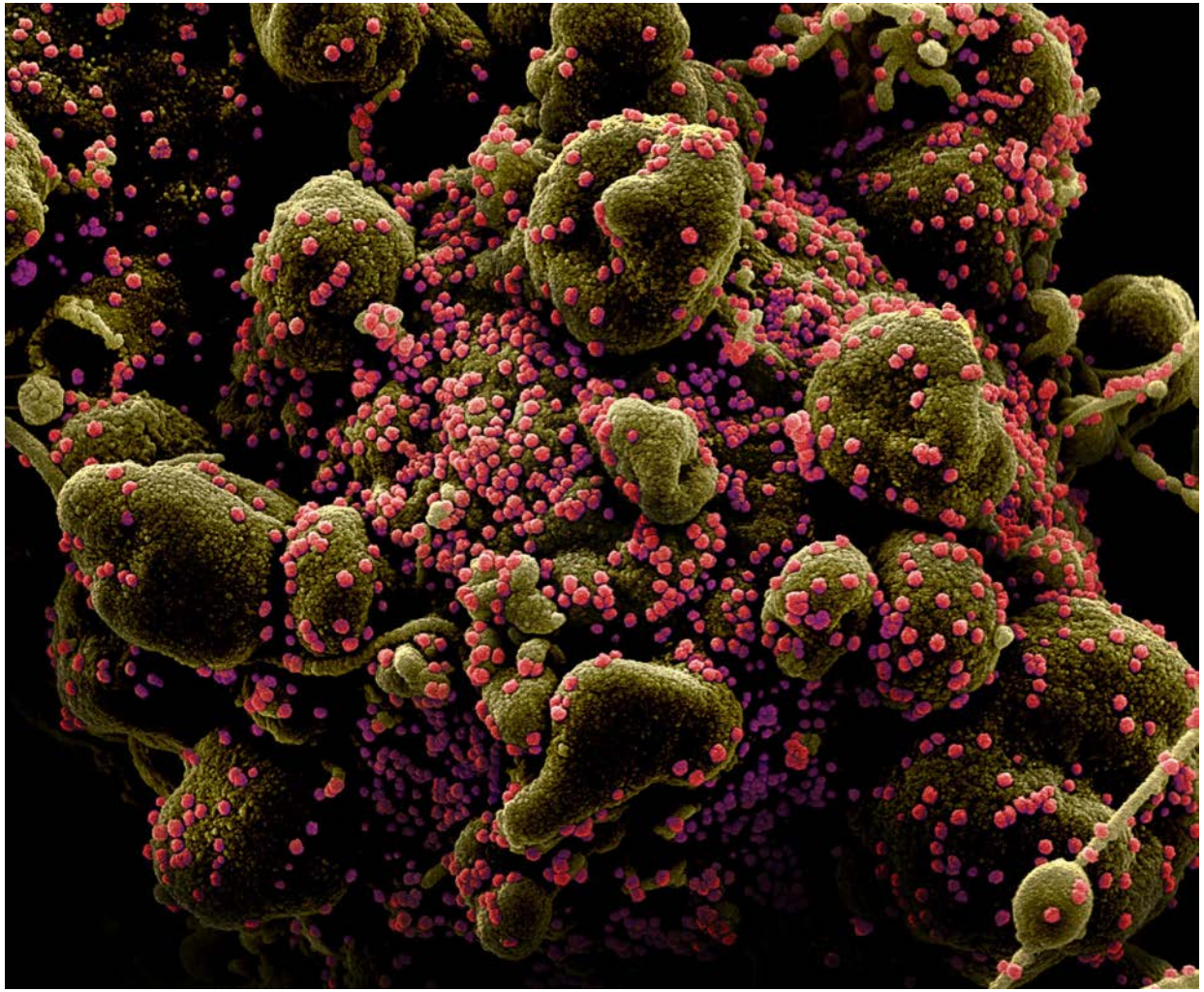
Nov 17, 2020

UCSF Center for Tobacco Control Research and Education

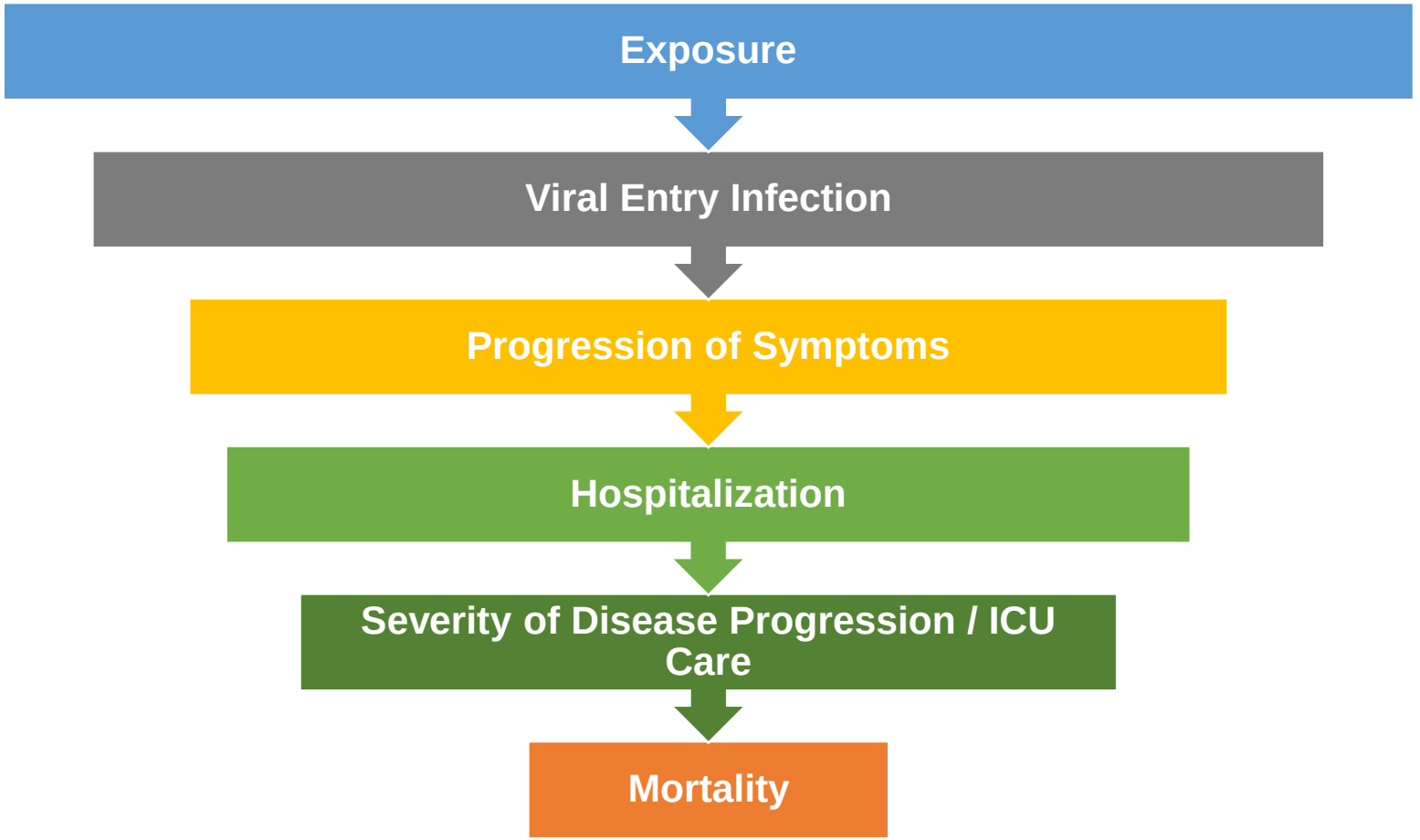
SARS-CoV-2


Envelope protein
Membrane protein
Spike protein
Nucleocapsid protein
Enclosing RNA
Lipid membrane
Manuel Bortoletti

SARS-CoV-2



Stages of COVID-19 Infection



Epidemiology Overview Regarding Smokers & COVID-19 Infection Meta-Analyses (Causation Still Controversial)

- **Smokers reported to be less likely to become infected** than never smokers [RR 0.73; (0.54-0.99); Simons]. **Smokers more likely to become infected**, but varies with socioeconomic status [Jackson]
- **Smokers less likely to be hospitalized** [6515 cases in China, US, S. Korea, Japan] ; prevalence odds ratio 0.24 (0.19 – 0.30; Farsalinos] **No difference in hospitalization** [RR 1.06;Simons]
- Current and former **smokers once hospitalized more likely to die** [RR 1.70, 1.14-2.55; RR 2.0, 1.57-2.55; Simons]

Potential Influences of COVID-19 on Smoking Behavior

Decreased Smoking

- Public messaging on harm
- Perception of increased risk
- COVID risk as teachable moment
- Disruption of daily smoking cues
- Less social smoking at home
- Home pressures not to smoke

Increased Smoking

- Coping with stress – isolation, financial, health concerns
- Difficulty getting cessation help
- Perception of protective effect of smoking
- Association with increased alcohol consumption

Impact of COVID-19 on Smoking Behaviors

Jackson … Addiction

- Smoking Toolkit study England
- Impact of lockdown (3/20)
- No change in CS prevalence
- Increased quit attempts (40 v 29%)
- Increased quit success (21 v 14%)
- Increased cessation (8.8 v 4.1%)
- No change in evidence-based but increased remote support

Klemperer … Tobacco Control

- Web-based survey dual TC/EC
- Changes due to COVID
- High concern TC increase health risk
- Motivation to quit incr 36% decr 16%
- 23% attempted quit to red harm
- 28% reduced use, 30% increased use
- Weak correlation between perceived harm and reduced use
- Similar behavioral for TC and EC

TC = Tobacco Cigarette
EC = Electronic Cigarette

Recommendations for Smoking and Nicotine Product Use in Relation to COVID-19

- Cigarette smoking is potentially life-threatening with or without COVID infection.
  - Smokers hospitalized with COVID do worse.
  - Smokers should be counseled to quit as soon as possible.
- Benefits vs risks of nicotine vaping unclear.
  - Some concerns about pro-inflammatory effects of thermal degradation products (oxidants and others) and PG/VG, but risk probably much less than cigarette smoking
- Smokeless tobacco use is probably not a concern, but no available data

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Panel Discussion