Enhancing Adoption of Innovative Clinical Trial Approaches

March 19, 2024 | 10:00 am – 5:00 pm ET
March 20, 2024 | 12:30 pm – 5:00 pm ET

FDA U.S. FOOD & DRUG ADMINISTRATION

Duke | MARGOLIS INSTITUTE *for* Health Policy

Welcome and Opening Remarks: Day 1

Mark McClellan

Director, Duke-Margolis Institute for Health Policy

Statement of Independence

The Robert J. Margolis, MD, Institute for Health Policy is part of Duke University, and as such it honors the tradition of academic independence on the part of its faculty and scholars. Neither Duke nor the Margolis Institute take partisan positions, but the individual members are free to speak their minds and express their opinions regarding important issues.

For more details on relevant institutional policies, please refer to the Duke Faculty Handbook, including the Code of Conduct and other policies and procedures. In addition, regarding positions on legislation and advocacy, Duke University policies are available at http://publicaffairs.duke.edu/government.

Workshop Agenda Day 1

10:00 AM	Welcome
10:10 AM	Fireside Chat
10:30 AM	Evolution of Clinical Trial Research and the Current State of Trial Innovation
11:30 AM	Break
11:40 AM	Regulatory and Compliance Considerations
12:55 PM	Lunch Break
2:10 PM	Patient-Centric and Recruitment Considerations
3:25 PM	Break
3:35 PM	Infrastructure and Organizational Considerations
4:50 PM	Closing Remarks

Workshop Agenda Day 2

12:30 PM	Welcome and Day 1 Recap
12:45 PM	Global Regulatory Collaboration on Clinical Trial Innovation
1:55 PM	Break
2:05 PM	Collaborations Across Industries to Leverage Innovation
3:20 PM	Break
3:30 PM	Future Directions on Clinical Trial Innovation
4:45 PM	Closing Remarks

Audience Participation

Fireside Chat

Mark McClellan, Duke-Margolis Institute for Health Policy

Patrizia Cavazzoni, U.S. Food and Drug Administration

Session 1: Evolution of Clinical Trial Research and the Current State of Trial Innovation

Moderator: **Mark McClellan, Duke-Margolis Institute for Health Policy**

Speakers:

Monica Bertagnolli, National Institutes of Health

Ned Braunstein, Regeneron

Esther Krofah, Milken Institute

Robert Metcalf, Eli Lilly

Janet Woodcock, U.S. Food and Drug Administration (Retired)

Patrizia Cavazzoni, U.S. Food and Drug Administration

Moderated Discussion and Audience Q&A

Moderator:

Mark McClellan

Duke-Margolis Institute for Health Policy

We Are Taking A Break…
Our Program Will Resume at 11:40 am ET

FDA has created a public docket (FDA-2023-N4489) to inform CDER's future work on clinical trial innovation

Submit your response by April 19:
https://www.regulations.gov/docket/FDA-2023-N-4489/document

Session 2: Regulatory and Compliance Considerations

Moderator: **Morgan Hanger,** Clinical Trials Transformation Initiative

Speakers:

Nicole Mayer Hamblett, Seattle Children's Research Institute (Cystic Fibrosis Foundation)

Bea Lavery, Genentech

Amy McKee, Parexel

Nancy Kass, Johns Hopkins University

Martin Landray, Protas and Good Clinical Trials Collaborative

M. Khair ElZarrad, U.S. Food and Drug Administration

Innovative Approaches to Progress a *Pipeline* of Therapies for Cystic Fibrosis

Nicole Mayer Hamblett, PhD

Co-Executive Director
CF Therapeutics Development Network Coordinating Center
Seattle Children's Research Institute

Professor, Pediatrics
Adjunct Professor, Biostatistics
University of Washington

CYSTIC FIBROSIS FOUNDATION
THERAPEUTICS
DEVELOPMENT NETWORK

CYSTIC FIBROSIS FOUNDATION®

Modulator Ineligible Population with CF: An Ultra-Rare Sub-Population

Nucleic acid-based therapy (NABT) approach will be needed to provide CFTR function

~1100

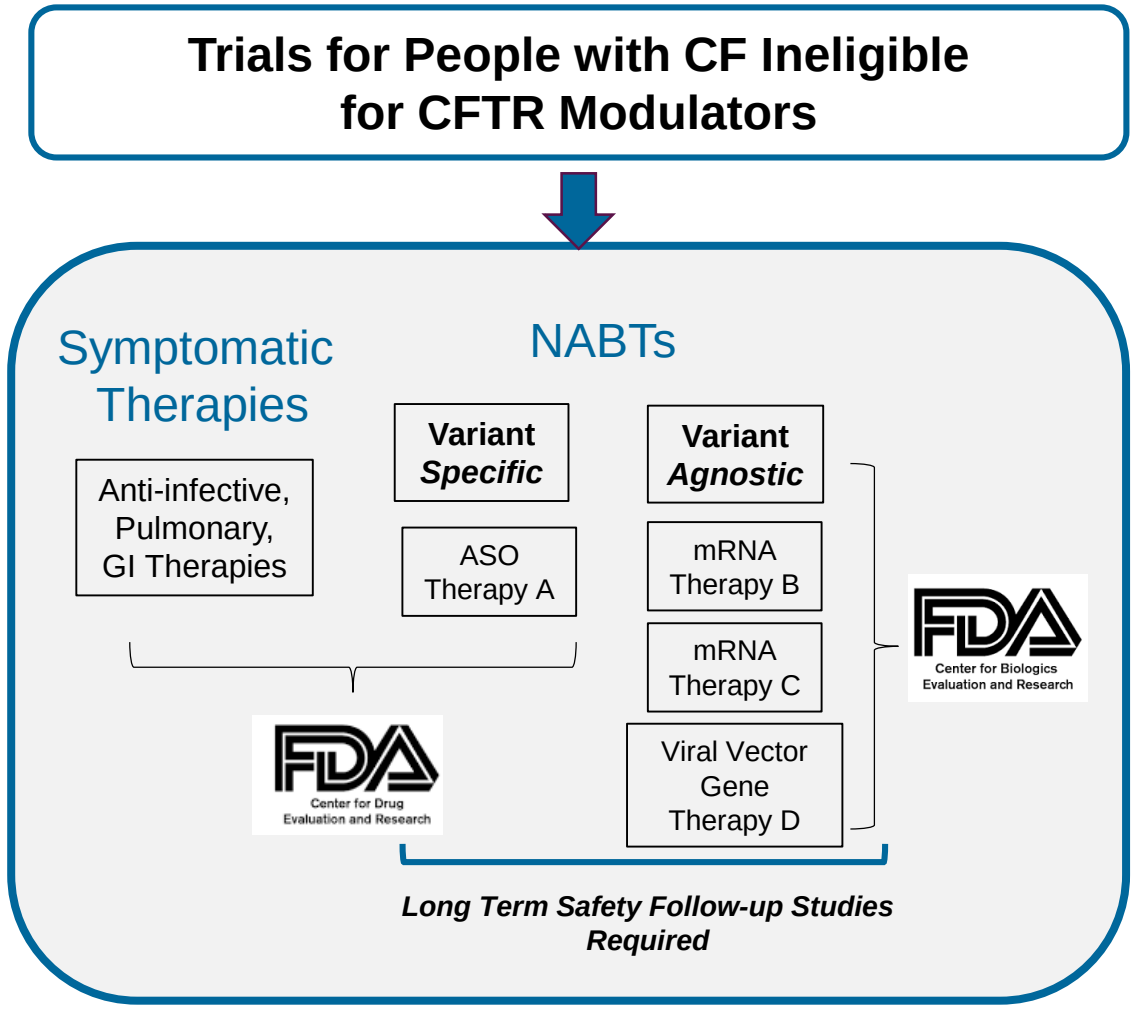
adults with CF ineligible for modulators

& ppFEV$_1$ 40% & no lung transplant

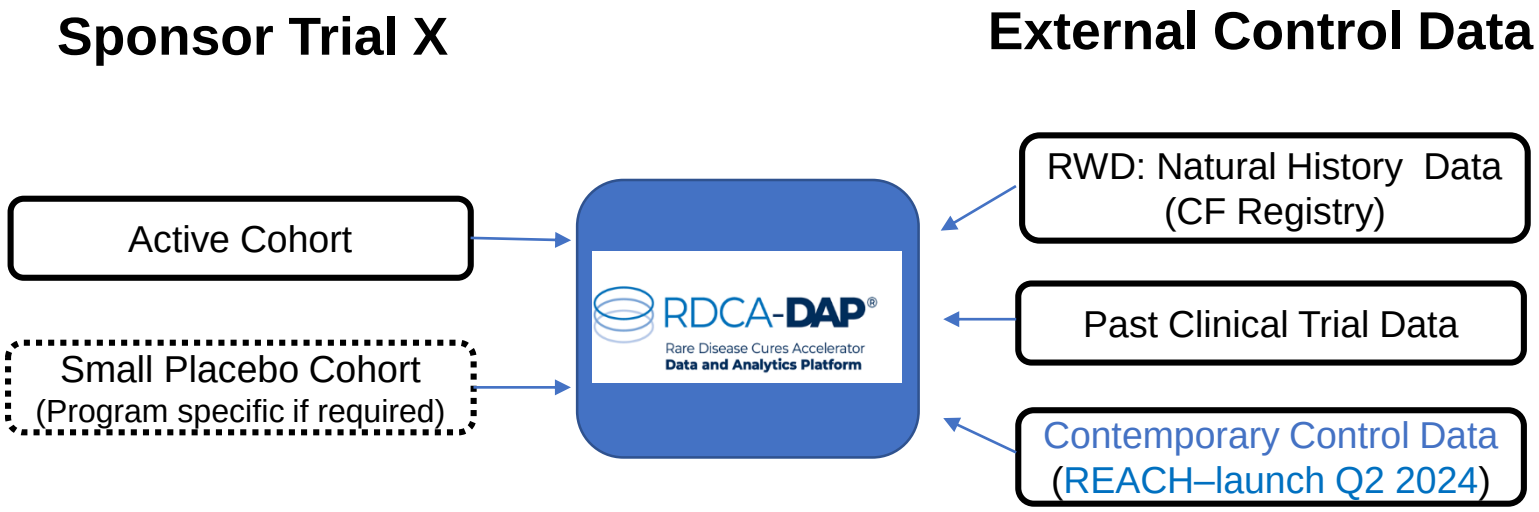
~25% are BIPOC and/or Hispanic

<25% with prior research trial experience

Trials for People with CF Ineligible for CFTR Modulators



Sponsor Agnostic "External Control" Study to Support Innovative Designs that Will Streamline Trial Sizes *Across the Pipeline*



Research Expansion to Advance the CF THerapeutic Pipeline for People with CF without Modulators: (REACH) Study (***CF Foundation Sponsored, PI: D. Polineni***)

- **Outcome data includes standardized NABT trial outcomes and time points of key interest**
- **Standardized comparative safety data and lab collection**
- **Onsite monitoring of study data, use of regulatory compliant data systems**
- **Conducted in the same trial network (TDN) as clinical trials**

COMMUNITY VOICE
CYSTIC FIBROSIS FOUNDATION

"Being able to substitute the data you have with REACH participants; I think that's groundbreaking."

Moderated Discussion and Audience Q&A

Moderator:

Morgan Hanger

Clinical Trials Transformation Initiative

We Are Taking A Break for Lunch…
Our Program Will Resume at 2:10 pm ET

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Session 3: Patient Centric and Recruitment Considerations

Moderator: **Jennifer Urwongse,** PPD

Speakers:

Jacqueline Corrigan-Curay, U.S. Food and Drug Administration

David Feldman, National Kidney Foundation

Pamela Tenaerts, Medable

Al Richmond, Community-Campus Partnerships for Health

Marilyn Metcalf, GSK

Moderated Discussion and Audience Q&A

Moderator:

Jennifer Urwongse

PPD

We Are Taking A Break…
Our Program Will Resume at 3:35 pm ET

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Session 4: Infrastructure and Organizational Considerations

Moderator: **Donna Cryer**, Global Liver Institute

Speakers:

Laura Esserman, University of California San Francisco

Anastasia Lesogor, Novartis

Cynthia Verst, IQVIA

Rob DiCicco, TransCelerate BioPharma

John Halamka, Mayo Clinic

David Burrow, U.S. Food and Drug Administration

Industry perspective on selective safety data collection in cardiovascular outcomes trials

Anastasia Lesogor, MD
Washington D.C.
March 19, 2024

NOVARTIS | Reimagining Medicine

Disclosure/Disclaimer

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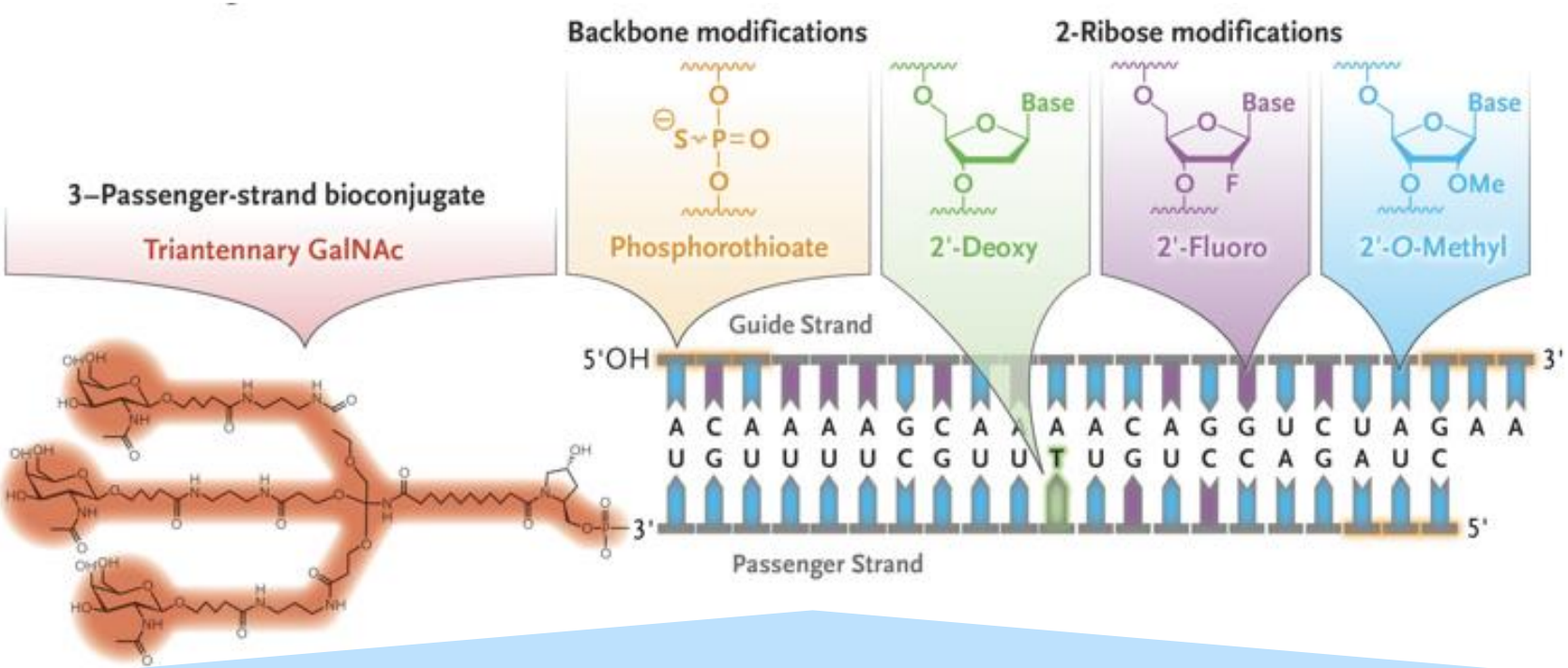
Inclisiran is the first small interfering ribonucleic acid (siRNA) cholesterol-lowering therapy for chronic use in a large patient population

Inclisiran Structure



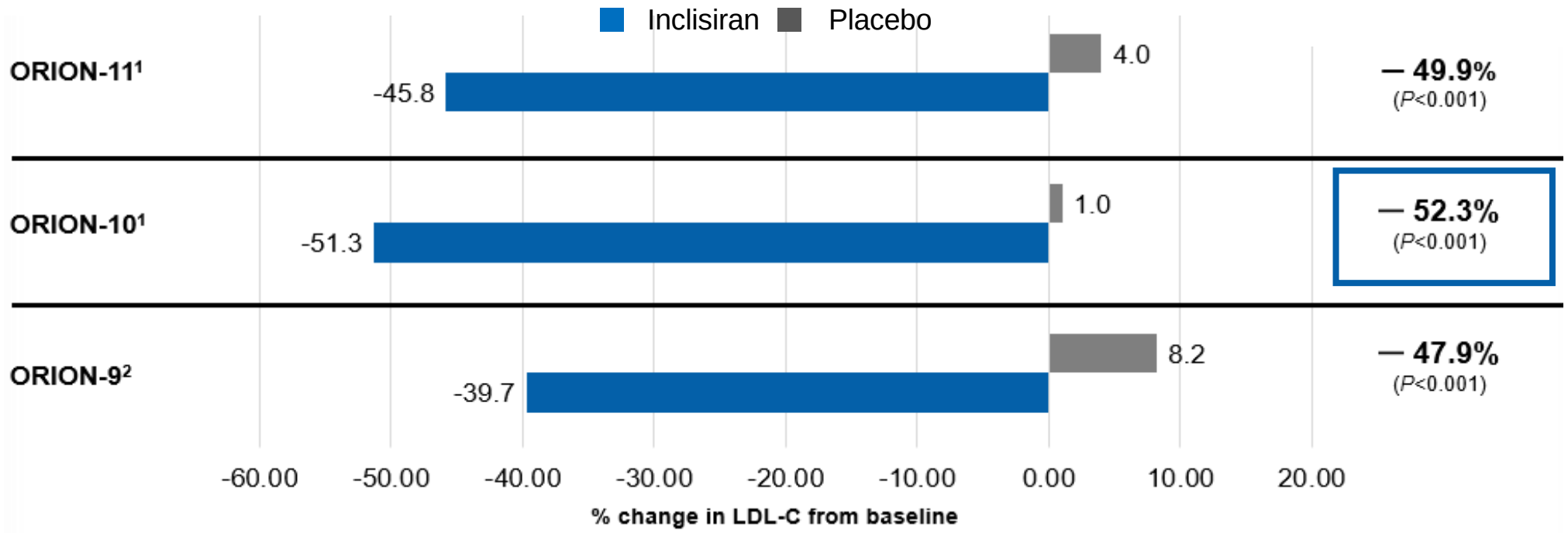
1. Prevents production of proprotein convertase subtilisin/kexin type 9 (PCSK9)
2. Greater hepatic uptake of circulating low-density lipoprotein cholesterol (LDL-C)
3. Reduction of LDL-C levels in the bloodstream

Sources: 1. Khvorova A.. N Engl J Med 2017; 376:4-7; 2. Fitzgerald K, et al. N Engl J Med 2017; 376:41-51.

Acronyms: GalNAc - *N*-acetylgalactosamine

In pivotal phase 3 studies, inclisiran demonstrated effective LDL-C reduction while being generally well-tolerated with twice-yearly* dosing

Inclisiran Phase 3 Studies: Impact on LDL-C Reduction



Inclisiran effected **significant reductions in LDL-C vs. placebo** at Day 510, on top of standard of care *(Range: -47.9%, -52.3%)*

**Inclisiran is dosed initially, again at 3 months, and then once every 6 months*

NOVARTIS | Reimagining Medicine

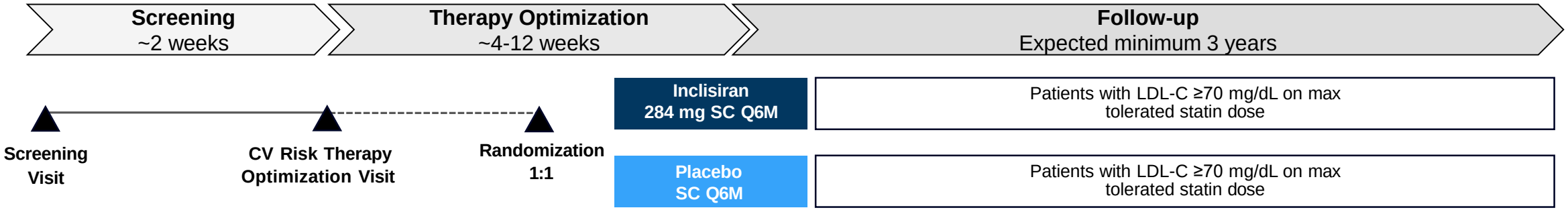
Sources: 1. Ray KK, et al. *N Engl J Med*.2020;382(16):1507-1519; 2. Raal FJ, et al. *N Engl J Med*.2020;382(16):1520-1530

Acronyms: ASCVD – Atherosclerotic cardiovascular disease LDL-C – Low-density lioprotein cholersterol

Study Patient Populations: ORION 11 – ASCVD Risk Equivalent; ORION-10 – ASCVD; ORION-9 - Heterozygous familial hypercholesterolemia

VICTORION-2-PREVENT (V2P) trial design is aligned with regulatory requirements to support an indication for cardiovascular risk reduction

VICTORION-2-PREVENT Trial Design



Patient Population	**Atherosclerotic cardiovascular disease** (prior myocardial infarction, ischemic stroke, symptomatic peripheral arterial disease); LDL-C ≥70mg/dL; all patients required to be on high-intensity statin
Sample Size	>17,000
Primary Endpoint	Time to first event of **3-point major adverse cardiovascular event** (3P-MACE): cardiovascular death, non-fatal myocardial infarction, and non-fatal ischemic stroke
Secondary Endpoints	• Time to occurrence of cardiovascular death • Time to first occurrence of 4P-MACE* • Time to first occurrence of major adverse limb events (MALE) • Time to occurrence of all-cause death • Safety & tolerability of inclisiran

**4P-MACE includes cardiovascular death, non-fatal MI, non-fatal ischemic stroke and urgent coronary revascularization*

Acronyms: LDL-C – Low-density lioprotein cholersterol; 4P-MACE – 4-point major adverse cardiovascular event

Selective safety data collection (SSDC) is widely accepted across geographies represented in the VICTORION-2-PREVENT sample

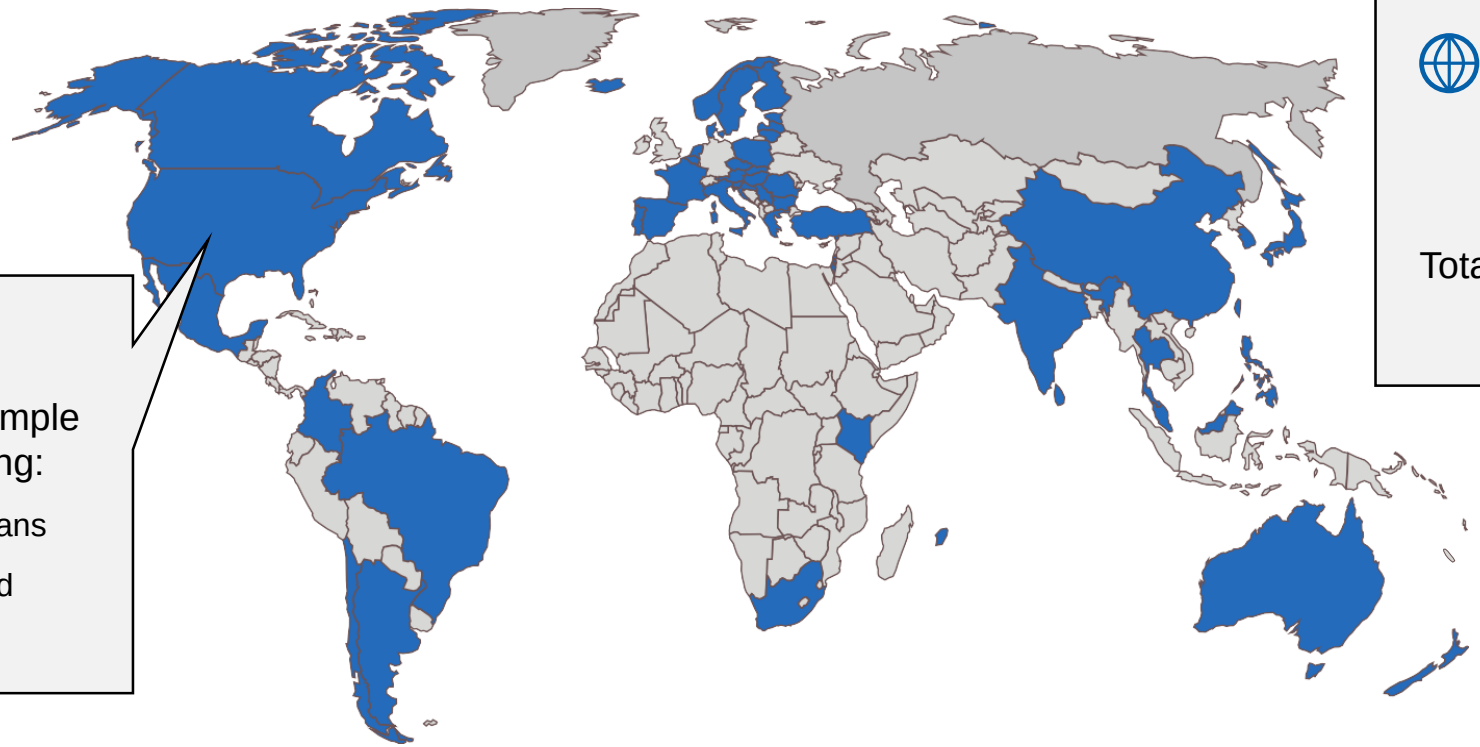
VICTORION-2-PREVENT Study Locations

US Footprint

17% of total study sample (N > 2,800) including:

~ 20% African-Americans

~ 17% Self-identified Hispanic/Latino



Global Footprint

40 Countries

>1,100 Study Sites

Total Sample Size **>17,000 Patients**

Recruitment Status: Completed, first patient first visit in November 2021

Our SSDC approach is supported by ICH & FDA guidance on SSDC in late-stage pre-approval or post-approval trials and inclisiran's well-characterized safety

December 2022: E19 A Selective Approach to Safety Data Collection in Specific Late-Stage Pre-Approval or Post-Approval Clinical Trials – Guidance for Industry[1]

Once a drug has been approved, comprehensive collection of all safety data may provide only limited additional knowledge of clinical importance. In such circumstances, a ***more selective approach to safety data collection may be adequate*** *as long as the trial objectives and the welfare of trial participants are not compromised*

The **safety profile of inclisiran is well characterized** in a similar patient population in pivotal clinical trials and post-marketing.

– *~46,361 patients in clinical trials; post-marketing experience* 135,295 *PTY as of Feb 2024*

Sources: 1. E19 A Selective Approach to Safety Data Collection in Specific Late-Stage Pre-Approval or Post-Approval Clinical Trials – Guidance for Industry

Acronyms: SSDC – Selective safety data collection

The safety assessments in VICTORION-2-PREVENT are close to those assessed in clinical practice

General Safety Assessments

- Serious adverse events (SAEs)
- Adverse events (AEs) leading to study treatment discontinuation
- AEs of special interest: new-onset diabetes mellitus (lipid-lowering therapy class effect)

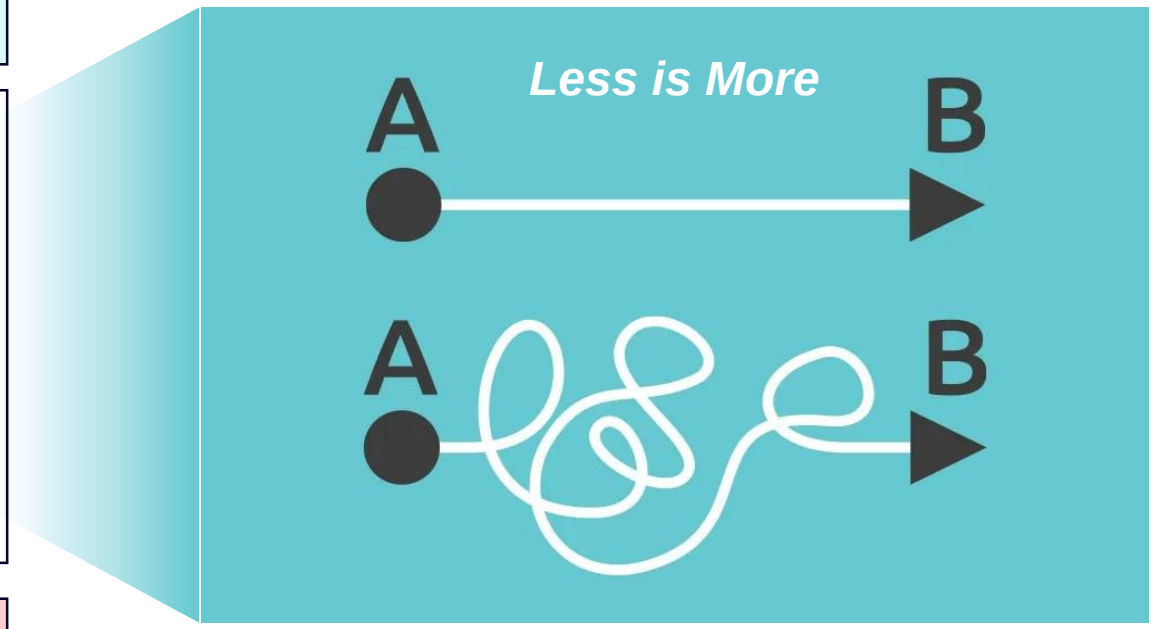
Central Lab Safety Assessments

- Hematology, biochemistry, urinalysis at screening only
- Blinded lipid panel every 12 months
- Liver function testing performed in 20% of randomized patients post-randomization

Taking a simpler approach to safety through SSDC has several benefits, including reducing study burden and closely resembling clinical practice

Opportunities

- Selective safety assessment is closer to real clinical practice
- Reduces burden on patients & investigators
- Reduces overall study cost
- Strong interest in trial & excellent recruitment rate
  - >17,000 patients enrolled in 23 months
  - 1.02 patient/site/month is above existing benchmarks (0.37-0.72)*



Challenges

- SSDC is in earlier stages of development

Sources: 1. Sabatine et al. *N Engl J Med*. 2017; Schwartz et al, *N Engl J Med*. 2017

Acronyms: SSDC – Selective safety data collection

Thank you

Moderated Discussion and Audience Q&A

Moderator:

Donna Cryer

Global Liver Institute

Closing Remarks: Day 1

Gerrit Hamre

Research Director, Duke-Margolis Institute for Health Policy

Thank You!

Contact Us

healthpolicy.duke.edu

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Overview of Day 1

- Fireside Chat
- Evolution of Clinical Trial Research and the Current State of Trial Innovation
- Regulatory and Compliance Considerations
- Patient-Centric and Recruitment Considerations
- Infrastructure and Organizational Considerations

Workshop Agenda Day 2

12:30 PM	Welcome and Day 1 Recap
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1:55 PM	Break
2:05 PM	Collaborations Across Industries to Leverage Innovation
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3:30 PM	Future Directions on Clinical Trial Innovation
4:45 PM	Closing Remarks

Audience Participation

Session 5: Global Regulatory Collaboration on Clinical Trial Innovation

Moderator: **Peter Stein,** U.S. Food and Drug Administration

Speakers:

Yuki Ando, Pharmaceuticals and Medical Devices Agency

Sarem Sarem, Health Canada

Andrew Thomson, European Medicines Agency

John Zhong, REGENXBIO (Pharmaceutical Research and Manufacturers of America)

M. Khair ElZarrad, U.S. Food and Drug Administration

Lucia D'Apote, Amgen (European Federation of Pharmaceutical Industries and Associations)

Moderated Discussion and Audience Q&A

Moderator:

Peter Stein

U.S. Food and Drug Administration

We Are Taking A Break…
Our Program Will Resume at 2:05 pm ET

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Session 6: Collaborations Across Industries to Leverage Innovation

Moderator: **Ryan Ferguson,** U.S. Department of Veteran Affairs

Speakers:

Angie Goldsberry, Biogen

Luke Kosinski, Critical Path Institute

Neal Meropol, Flatiron Health

Stacey Adam, Foundation for the National Institutes of Health

Jeff Allen, Friends of Cancer Research

John Concato, U.S. Food and Drug Administration

Moderated Discussion and Audience Q&A

Moderator:

Ryan Ferguson

U.S. Department of Veteran Affairs

We Are Taking A Break…
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Session 7: Future Directions on Clinical Trial Innovation

Moderator: **Kevin Bugin,** U.S. Food and Drug Administration

Speakers:

Richard Schilsky, Reagan-Udall Foundation for the FDA

Amy Bertha, Bayer (Biotechnology Industry Organization)

Micky Cohen-Wolkowiez, Duke Clinical Research Institute

Amy Abernathy, Verily

Craig Lipset, Decentralized Trials and Research Alliance

Martin Mendoza, National Institutes of Health

Integrating Post-Market Clinical Studies Into Health Care Delivery: Project Mandate

Development of a post-market evidence generation framework that

- leverages the U.S. health care system to resolve clinically meaningful evidence gaps for medical products
- supports regulatory submissions for new indications or other revisions to labeling

- Greater clinician engagement
- Broader patient participation
- Acceptance of pragmatic, post-market clinical studies
- Collection of routine clinical data within the context of health care delivery

Overarching Recommendations

- Simplify evidence generation in the post-market setting, including
  - Protocol objectives and endpoints
  - Eligibility criteria
  - Adverse event reporting
  - Data collection

- Doing so will
  - Reduce administrative requirements, site and clinician credentialing
  - Encourage greater participation by both clinicians and patients

- Articulate the "value proposition" for healthcare leaders to support post-market EvGen

Embedded in clinical care

Person-centered research objectives

Simple study design

Streamline required data collection; use standard data elements

Rapid dissemination/uptake of findings

Specific Recommendations for FDA

REAGAN-UDALL FOUNDATION FOR THE FDA

- Inter-agency taskforce to establish guiding principles for evidence generation
- Establish a lexicon for post-market evidence generation studies
- Accept pragmatic, post-market studies to support expanded indications, label changes, etc.
- Simplify site-related documentation and investigator credentialing*
- Guidance on validation and use of algorithms to identify endpoints derived from real-world data (RWD)
- Analysis of adverse events at end of study using RWD

*FDA recently issued final guidance or draft guidance of relevance

Recommendations for FDA (cont'd)

- More guidance on scope, scale and quality of evidence needed to expand indications, modify labeling or close evidence gaps
- Pragmatic evidence generation principles promulgated and implemented throughout FDA
- Minimal data collection use cases and pilot demonstration projects*
- Clarification and guidance on necessary elements of informed consent*
- Include consent forms in ClinicalTrials.gov registration

*FDA recently issued final guidance or draft guidance of relevance

Moderated Discussion and Audience Q&A

Moderator:

Kevin Bugin

U.S. Food and Drug Administration

Closing Remarks: Day 2

Gerrit Hamre

Research Director, Duke-Margolis Institute for Health Policy

Thank You!

Contact Us

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