# On The RISE: Controls in Rare Disease Clinical Trials for Small and Diminishing Populations

September 3, 2025 | 9:30 am – 4:00 pm ET

Duke | MARGOLIS INSTITUTE for Health Policy

healthpolicy.duke.edu

# Welcome

**Gerrit Hamre**, 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.

*This project is supported by the Food and Drug Administration (FDA) of the U.S. Department of Health and Human Services (HHS) as part of a financial assistance award [U19FD006602] totaling $5,192,495 with 100 percent funded by FDA/HHS. The contents are those of the author(s) and do not necessarily represent the official views of, nor an endorsement, by FDA/HHS, or the U.S. Government.*

# Event Agenda

| | |
|---|---|
| **9:30 am** | Welcome |
| **9:35 am** | Opening Remarks |
| **10:00 am** | Session 1: Considerations for Control Decisions |
| **11:00 am** | Break |
| **11:15 am** | Session 2: Internal Control Options |
| **12:30 pm** | Lunch Break |
| **1:45 pm** | Session 3: External Control Options |
| **3:00 pm** | Break |
| **3:15 pm** | Session 4: Where do we go from here? |
| **3:55 pm** | Closing Remarks and Adjournment |

All times listed in ET

# Logistics

Questions

- All attendees are encouraged to submit questions via Zoom or Slido and add comments in the chat if desired.
- In-person attendees may also raise their hand and someone from the Duke-Margolis team will hand you a mic

Technology Issues?

- Please type your issue in the Q&A or email us at margolisevents@duke.edu

All meeting materials for this workshop will be available on the Duke-Margolis website

Duke
MARGOLIS INSTITUTE for Health Policy

Join at

**slido.com**

**#RISE**

# Opening Remarks

**Vinay Prasad**, CBER, U.S. Food and Drug Administration

**George Tidmarsh**, CDER, U.S. Food and Drug Administration

**Amy Comstock Rick**, RDIH, U.S. Food and Drug Administration

# Session 1: Considerations for Control Decisions

10:00 – 11:00 am ET

**Moderator:** Gerrit Hamre, Duke-Margolis Institute for Health Policy

# Session 1: Considerations for Control Decisions

*Moderator:*

- **Gerrit Hamre**, Duke-Margolis Institute for Health Policy

*Panelists:*

- **Stacey Frisk**, Rare Disease Company Coalition
- **Cara O'Neill**, Cure Sanfilippo Foundation
- **Marshall Summar**, Uncommon Cures, LLC
- **Karmen Trzupek**, Global Genes

Duke
MARGOLIS INSTITUTE for Health Policy

Join at
slido.com
#RISE

# Moderated Discussion and Q&A

**Moderator:** Gerrit Hamre, Duke-Margolis Institute for Health Policy

# BREAK

## Our Program Will Resume at 11:15 AM ET

Scan to Register

**Best Practices and Lessons Learned from the Chemistry, Manufacturing, and Controls (CMC) Development and Readiness Pilot (CDRP) Program**

**September 10, 2025** • 1:00 - 4:45 pm ET

Duke | MARGOLIS INSTITUTE *for* Health Policy

*A Virtual Public Workshop*

## Upcoming Duke-Margolis Virtual Public Workshop

**September 10, 2025|1:00 – 4:45 PM ET**

Visit healthpolicy.duke.edu/events

# Session 2: Internal Control Options

11:15 – 12:30 pm ET

**Moderator:** Rachel Sher, Manatt, Phelps & Phillips, LLP

# Sanofi case study: Use of intra-patient comparison in severe Hemophilia A (congenital FVIII deficiency), a rare coagulation disorder

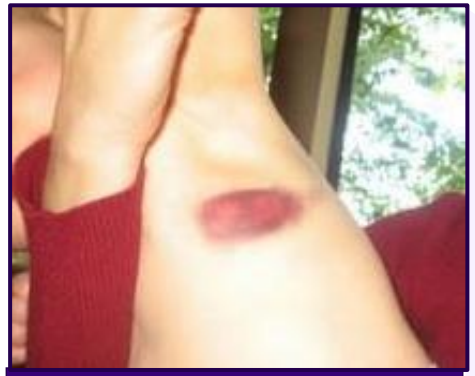
*Todd Paporello, Vice President, Global Head of Regulatory Affairs, Specialty Care*

sanofi

# Hemophilia A

- Hemophilia A is an inherited bleeding disorder, carried on the X chromosome, primarily affecting males and characterized by a deficiency of coagulation factor VIII.

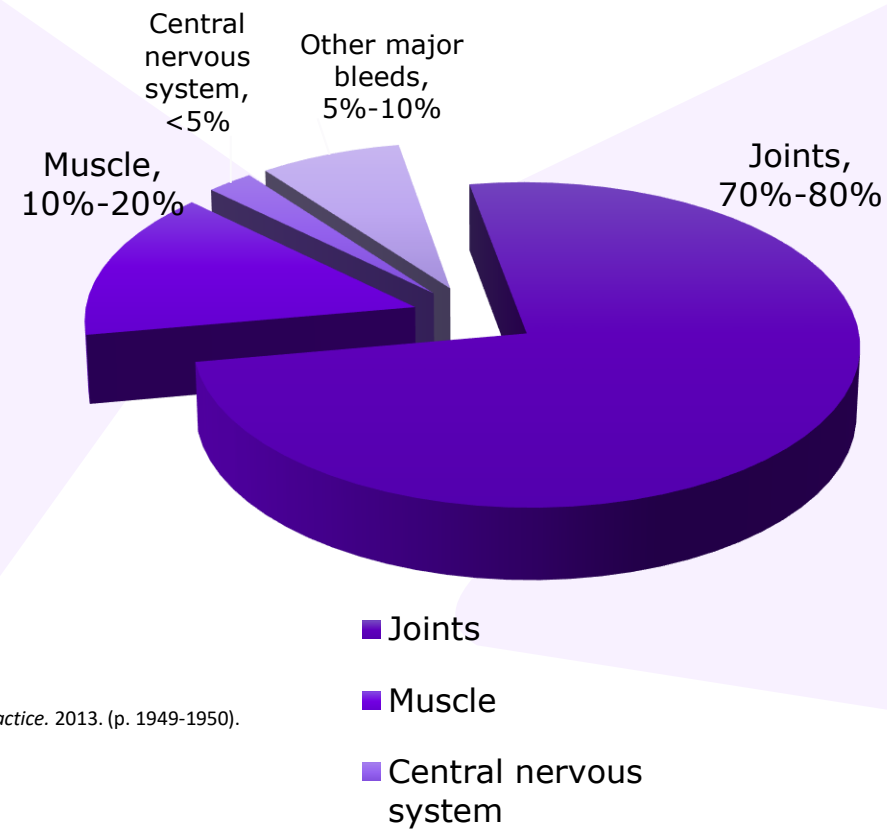
- When factor VIII is deficient or dysfunctional, the rest of the coagulation cascade cannot be appropriately activated and affect the process of clot formation

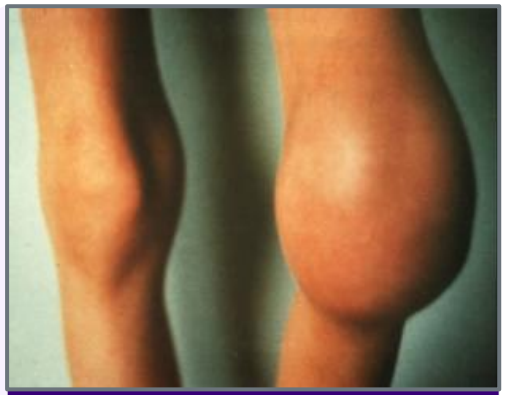


**Soft Tissue/ Muscle Bleeds[1]**

- Often accompanied by bruising
- Most common in the calf, thigh, buttocks, and forearms

**Incidence of bleeding by site[2]**



**Hemoarthroses (joint bleeds)[1]**

- Typically in ankles, knees, and elbows
- Accompanied by pain, swelling, and reduced mobility
- Can recur at a single joint (target joint)


1. Carcao et al. Hemophilia A and B. In: *Hematology: Basic Principles and Practice.* 2013. (p. 1949-1950).
2. Srivastava et al. *Haemophilia*. 2012;1-47. (p. 5).


sanofi

# ALTUVIIIO® (efanesoctocog alfa)

**APPROVED by the FDA in Feb 2023** in adults and children for:

- routine prophylaxis
- on-demand treatment and control of bleeding episodes
- perioperative management of bleeding

- Specifically designed to maintain high sustained FVIII activity levels with prolonged half-life. Can be dosed once weekly which contribute to reduced treatment burden compared to existing factor VIII replacement therapies.

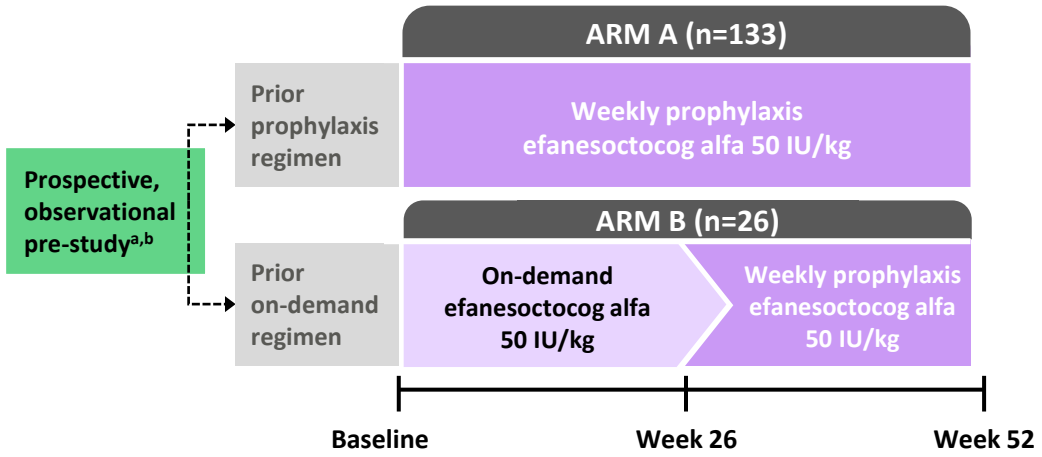
- Significant benefits over approved therapies recognized by Health Authorities as ALTUVIIIO was granted numerous Orphan Designations and Accelerated Pathways.

| | Orphan Status | Accelerated Pathway |
|---|---|---|
|  | ✓ Orphan | ✓ Fast track<br>✓ Breakthrough Designation<br>✓ Priority Review |
|  | ✓ The only FVIII replacement therapy with ODD | |
|  | ✓ The only FVIII replacement therapy with orphan status | ✓ Global Innovative products on Fast Track (GIFT) |
|  | ✓ Orphan | |

# XTEND-1: An Open-Label, Multicenter, Phase 3 Study of Efanesoctocog Alfa in Previously Treated Patients

## Key eligibility criteria

- Adult and adolescent patients (≥12 years) with severe hemophilia A
- Previous treatment with any recombinant and/or plasma-derived FVIII, or cryoprecipitate for ≥150 EDs




## Primary endpoint

**ABR in the prophylaxis treatment arm (ARM A)**

## Secondary endpoints

**Intra-patient ABR comparison (key secondary endpoint)[c]**

- Joint health outcomes (HJHS, target joint, joint US imaging[d])
- QoL (PROs, physical activity tracking[d])
- Efanesoctocog alfa consumption
- Treatment of bleeds
- Perioperative management
- Safety and tolerability
- PK

Permission to reuse image provided by von Drygalski A.
ABR, annualized bleed rate; EDs, exposure days; FVIII, factor VIII; HJHS, Hemophilia Joint Health Score; PK, pharmacokinetics; PRO, patient-reported outcome; QoL, quality of life; US, ultrasound.
[a]Prospective pre-study is Study 242HA201/OBS16221. [b]A total of 92 patients rolled over from the observational pre-study into XTEND-1, including 82 patients into Arm A and 10 into Arm B. [c]ABR during the efanesoctocog alfa weekly prophylaxis treatment period versus ABR during pre-study prophylaxis from the prior prospective observational study (Study 242HA201/OBS16221). [d]Exploratory endpoint.

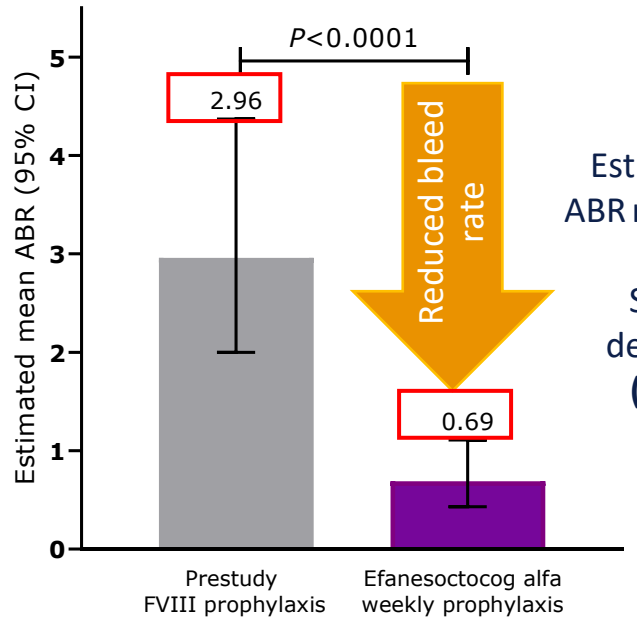
# Efanesoctocog Alfa Prophylaxis Provided Highly Effective Protection Against Bleeds, Superior to Prior FVIII Therapy

## Key secondary endpoint: Methods

- The key secondary efficacy endpoint was the mean paired difference between ABR for Arm A versus pre-study prophylaxis.
- The analysis included a subset of patients who participated in a prospective, observational pre-study and who had at least 6 months of available efficacy data from both the pre-study and XTEND-1.
- Non-inferiority and superiority of efanesoctocog alfa prophylaxis to pre-study prophylaxis were evaluated sequentially.

## Key secondary endpoint: Results

**Intra-patient ABR comparison (n=78)**




Estimated mean ABR reduction: **77%**

Superiority demonstrated (***P*<0.0001**)

| | Prestudy FVIII prophylaxis | Efanesoctocog alfa weekly prophylaxis |
|---|---|---|
| **Median ABR (IQR)** | 1.06 (0.00–3.74) | 0.00 (0.00–1.04) |

ABR, annualized bleed rate; CI, confidence interval; FVIII, factor VIII; IQR, interquartile range.

sanofi

# Addressing the Challenges of Rare Disease Research

**In rare diseases like hemophilia A, traditional randomized controlled trials (RCTs) face limitations due to:**

- Small patient populations
- Ethical concerns with placebo or suboptimal treatment arms
- High interpatient variability in bleeding phenotype and treatment response

**Leveraging Intra-patient Comparison: Enhancing Sensitivity and Reducing Variability**

- The key secondary endpoint of XTEND-1 was an Intra-patient comparison of annualized bleeding rate (ABR) between:
  - The **pre-study period** (standard-of-care FVIII prophylaxis) captured in the prospective observational study
  - The **interventional period** (once-weekly efanesoctocog alfa prophylaxis)

- **This design:**
  - Controls for interpatient variability in baseline bleeding risk
  - Enhances statistical power despite a modest sample size
  - Provides a **clinically meaningful benchmark** for assessing treatment benefit.

sanofi

# Regulatory History and Endpoint Negotiations with FDA

| | |
|---|---|
| **Prophylaxis vs. "On-Demand" outdated** | Insufficient for newer therapies, especially in previously treated patients already on prophylaxis (being the Standard of Care for most US patients).<br><br>Agreement with health authorities on ABR as primary endpoint. |
| **Intra-patient Comparison** | Intra-patient comparison approach viewed as more clinically relevant and sensitive to detect incremental improvements in bleed protection; **Enhanced Sensitivity & Reduced Variability** |
| **Observational pre-study** | Ensured **baseline** data integrity without intervention bias; provided flexibility and operational speed for Ph3 enrolment |

sanofi

# Future Considerations for Rare Disease Drug Development

- **Intra-patient comparisons** can be leveraged in small populations in order to support regulatory decisions.
- More **frequent interaction** with Health Authorities would be useful to avoid mis-steps.
- **Leverage observational studies** to reflect real-world treatment patterns and support clinical study design and potentially labeling.
- Pre-discuss with Health Authorities to set realistic **expectations on what can ultimately be claimed** in the label.
- Enhanced regulatory **alignment between divisions and centers** (CBER/CDER) reviewing the same disease areas to prevent inconsistent sponsor guidance and varying acceptance of labeling claims.
- **Global alignment** important among Health Authorities (FDA, EMA, Health Canada) regarding the relevance and importance of various endpoints.

# Session 2: Internal Control Options

*Moderator:*

- **Rachel Sher**, Manatt, Phelps & Phillips, LLP

*Presentation:*

- **Todd Paporello**, Sanofi

*Panelists:*

- **Allyson Berent**, Foundation for Angelman Syndrome Therapeutics
- **Rebecca Rothwell Chiu**, CDER, U.S. Food and Drug Administration
- **Jenn McNary**, Patient Advocate, Canary Advisors LLC
- **Adora Ndu**, BridgeBio
- **Tingting Zhou**, CBER, U.S. Food and Drug Administration

Duke
MARGOLIS INSTITUTE for Health Policy

Join at
slido.com
#RISE

# Moderated Discussion and Q&A

**Moderator:** Rachel Sher, Manatt, Phelps & Phillips, LLP

# LUNCH BREAK

## Our Program Will Resume at 1:45 PM ET

Scan to Register


# Upcoming Duke-Margolis Hybrid Public Workshop

**September 17, 2025|9:30 – 2:30 PM ET**

Visit healthpolicy.duke.edu/events

# Session 3: External Control Options

1:45 – 3:00pm ET

**Moderator:** Rachele Hendricks-Sturrup, Duke-Margolis Institute for Health Policy

CRITICAL PATH INSTITUTE 20 YEARS OF IMPACT

# The Value of Natural History Studies: The Givinostat Case Study

***Ramona Belfiore-Oshan, Ph.D.***
*Executive Director, Duchenne Regulatory Science Consortium*

*September 3rd, 2025*

# Why External Evidence Matters in Rare Disease

CRITICAL PATH INSTITUTE 20 YEARS

Small trials, ethical limits on placebo

DMD progression is heterogeneous

External controls contextualize and extend trial data

# Givinostat & Regulatory Milestones

HDAC inhibitor for ambulant DMD ≥6 years

EPIDYS Phase 3 trial: 72 weeks, 2:1 randomization

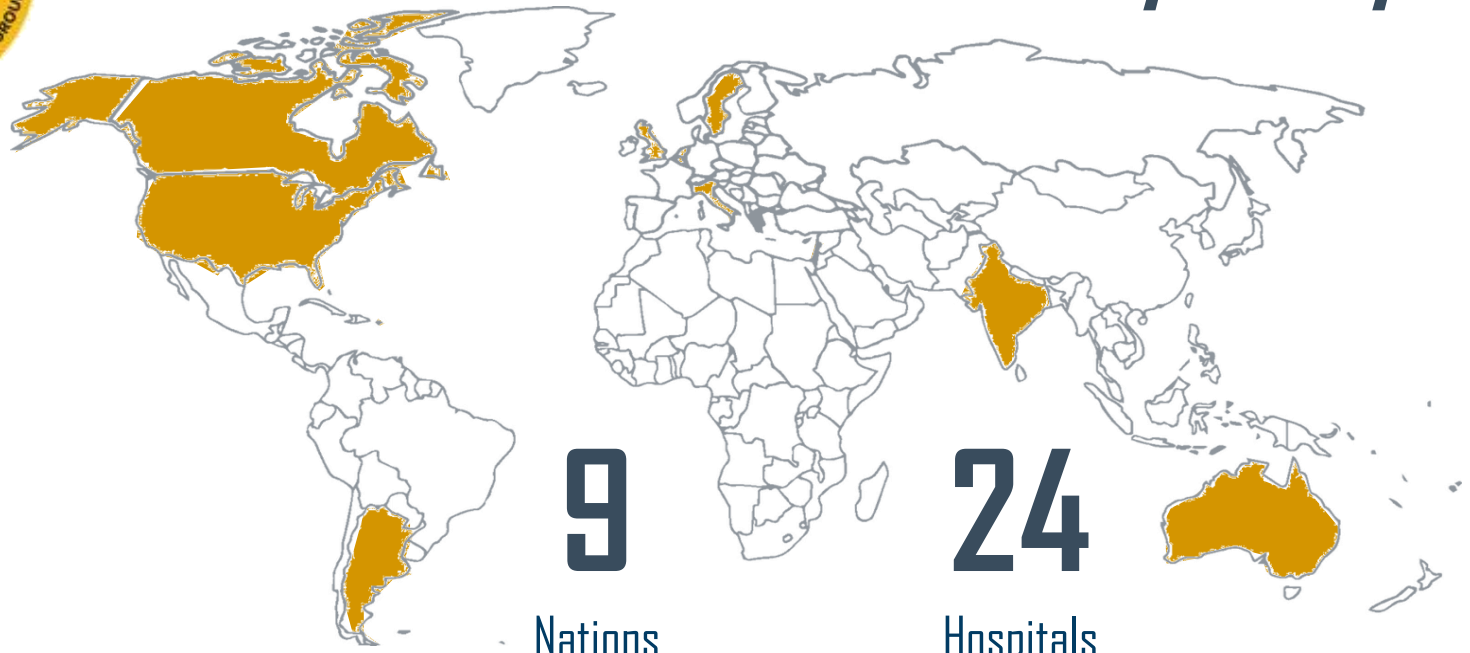
FDA: full approval (2024)

EMA: conditional marketing authorization ( 2025)

# CINRG DNHS Overview

Cooperative International Neuromuscular Research Group (CINRG)

## Duchenne Natural History Study



**9** Nations

**24** Hospitals

**440** Families

**>3500** Patient Visits

**>150** Researchers

Courtesy of Dr. Erik Henricson at UC Davis

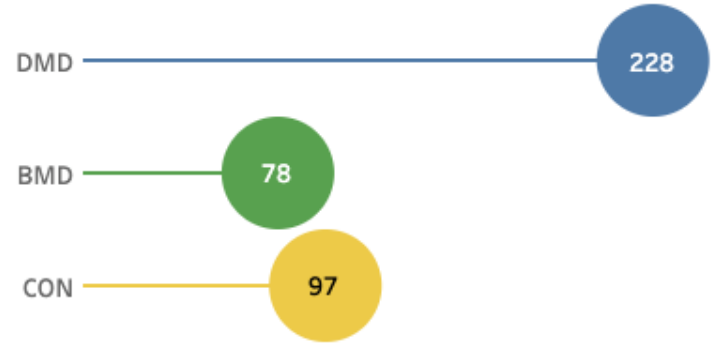
## Original DNHS 2005 - 2016

Sociodemographic Info
Genetic / Molecular Diagnostics
Biomarker Sampling
Health Conditions
*Cardiac*
*Pulmonary*
*Musculoskeletal*
*Gastrointestinal*
Medical Care Utilization
Medication Use
Anthropometrics
Strength and Mobility
Pulmonary Function
Activities & Participation
Health-related QoL
Sleep
Life Satisfaction
Caregiver QoL

# ImagingNMD NH Study Overview

imagingnmd.org/
research-dashboard

- 2010-present
- Florida, Oregon, Pennsylvania

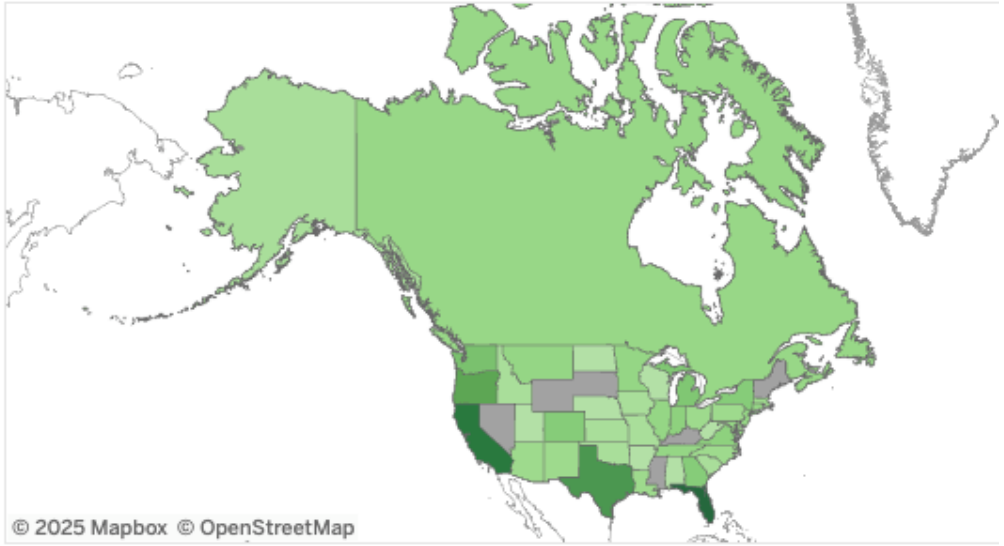


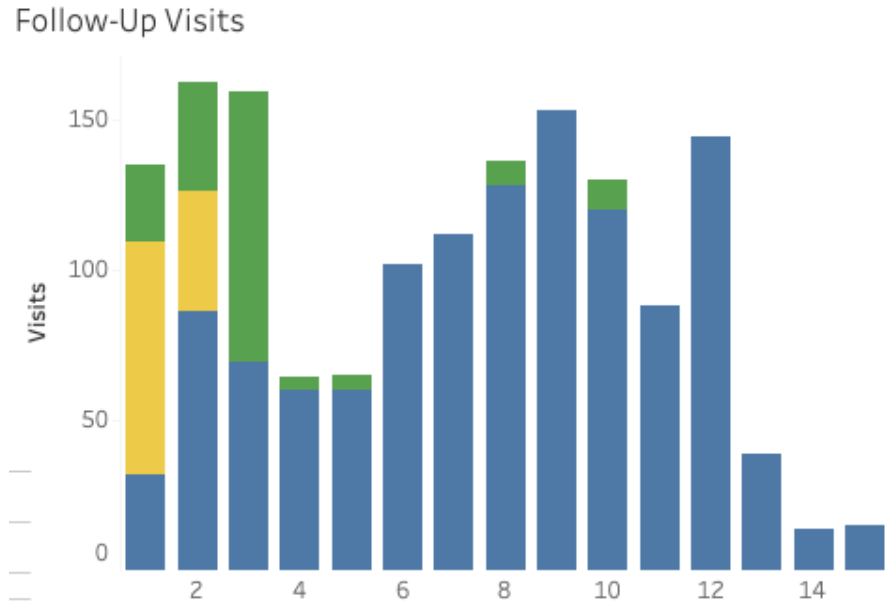

**Total Subjects**

403

**Total Visits**

1,520




Courtesy of Dr. Krista Vandenborne at ImagingNMD

# EPIDYS Trial Design

Primary endpoint: 4-stair climb

Baseline Vastus Lateralis Fat Fraction stratification (≤5%, 5–30%, >30%)

Secondary: Magnetic Resonance outcomes and timed functions

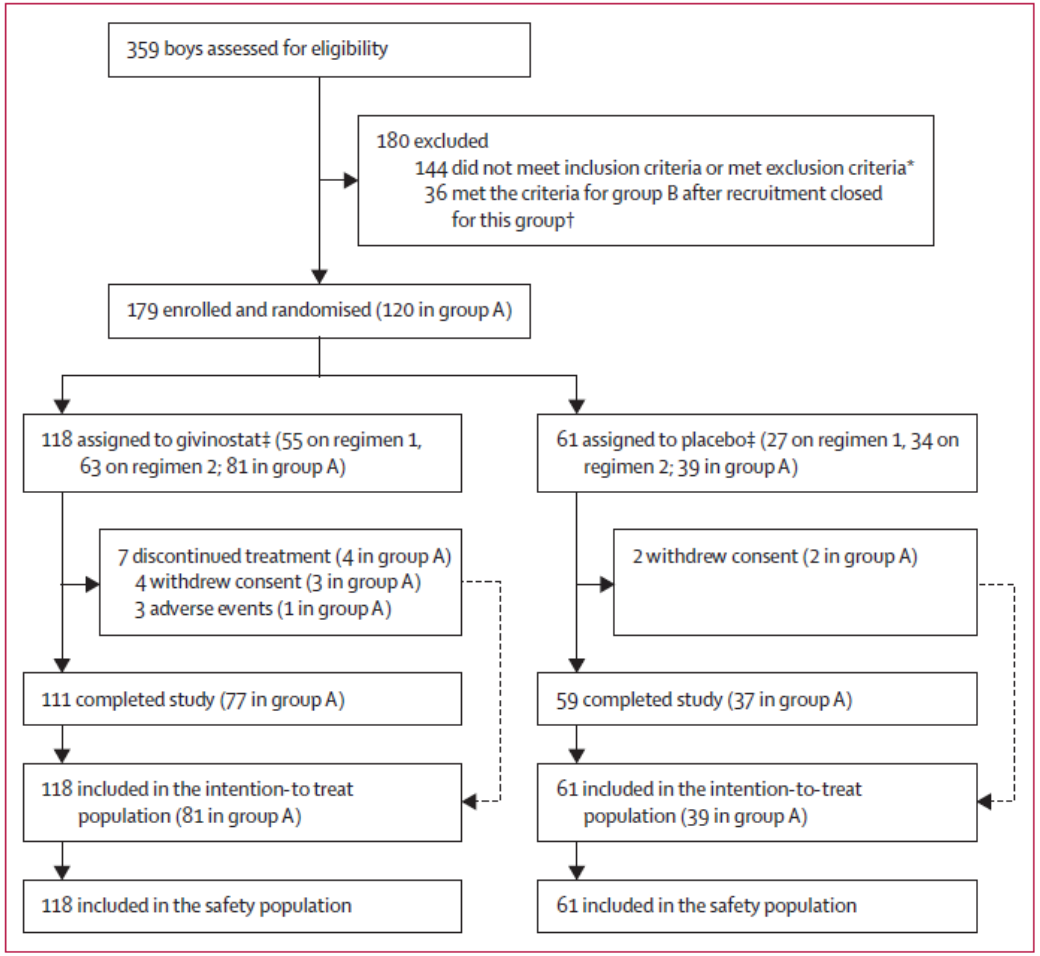
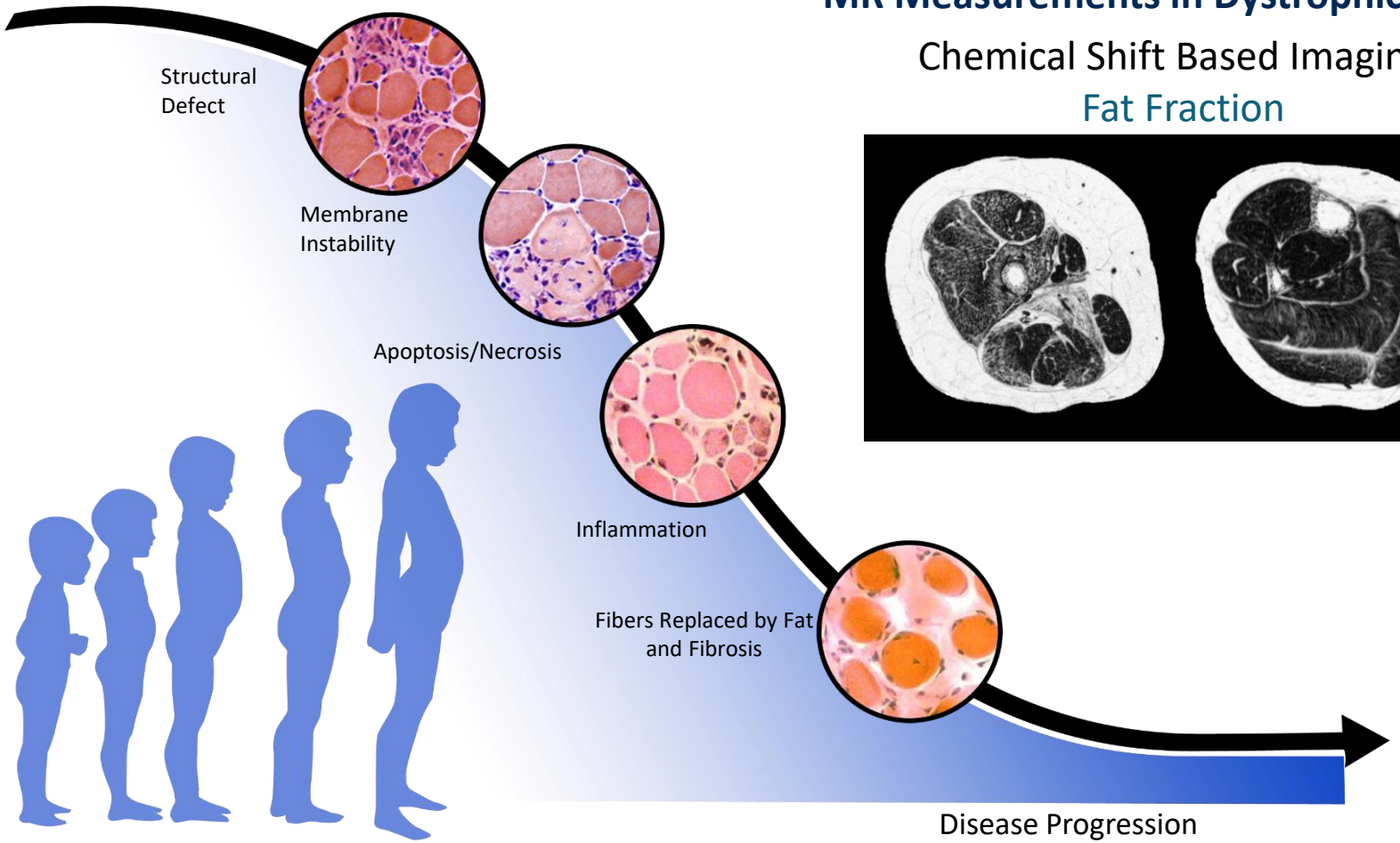



*Figure 1:* **Trial profile**

Ref: Mercuri, E., Vilchez, J. J., Boespflug-Tanguy, O., Zaidman, C. M., Mah, J. K., Goemans, N., Müller-Felber, W., Niks, E. H., Schara-Schmidt, U., Bertini, E., Comi, G. P., Mathews, K. D., Servais, L., Vandenborne, K., Johannsen, J., Messina, S., Spinty, S., McAdam, L., Selby, K., Byrne, B., … EPIDYS Study Group (2024). Safety and efficacy of givinostat in boys with Duchenne muscular dystrophy (EPIDYS): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. *The Lancet. Neurology*, *23*(4), 393–403. https://doi.org/10.1016/S1474-4422(24)00036-X

# ImagingDMD's Influence on EPIDYS




**MR Measurements in Dystrophic Muscle**

Chemical Shift Based Imaging:

Fat Fraction



VLFF stratification reduced heterogeneity

MR derived longitudinal measures provided mechanistic support

Courtesy of Dr. Krista Vandenborne at ImagingNMD

# Regulatory Use of External Evidence

- Accepted NH data as confirmatory evidence
  - Division of Epidemiology I (DEPI-I) agreed with using the integrated analysis of long-term efficacy with natural history data as confirmatory evidence of effectiveness for givinostat.

- Propensity Score Matching
  - Attempted to balance givinostat vs NH

# Quantitative Findings

EPIDYS: slower 4SC decline

Imaging: less VLFF progression vs placebo

NH comparisons: 1.6–3.5 year delays in functional losses

| | Standardised treatment effect (95% CI) | Least squares mean change from baseline (95% CI) | | |
|---|---|---|---|---|
| | | Givinostat* (n=81) | Placebo* (n=39) | Treatment effect |
| **Function** | | | | |
| Four-step climb | 2·14 (0·16 to 4·12) | 1·27 (1·17 to 1·37) | 1·48 (1·32 to 1·66) | 0·86 (0·75 to 0·99) |
| NSAA total score | 2·34 (0·36 to 4·33) | −2·66 (−3·56 to −1·76) | −4·58 (−5·89 to −3·26) | 1·91 (0·30 to 3·53) |
| Cumulative loss of function | 2·32 (0·36 to 4·28) | 3·42 (2·69 to 4·33) | 5·56 (4·00 to 7·72) | 0·61 (0·41 to 0·93) |
| Time-to-rise, s | 1·03 (−0·95 to 3·01) | 9·33 (5·82 to 12·84) | 12·61 (7·49 to 17·72) | −3·28 (−9·57 to 3·02) |
| 6-min walk test, m | 0·90 (−1·09 to 2·88) | −38·4 (−50·7 to −26·2) | −48·4 (−66·3 to −30·5) | 10·0 (−12·1 to 32·0) |
| **Strength** | | | | |
| Knee extension, N/kg | 1·71 (−0·27 to 3·69) | −0·32 (−0·44 to −0·20) | −0·50 (−0·68 to −0·33) | 0·19 (−0·03 to 0·40) |
| Elbow flexion, N/kg | 1·34 (−0·64 to 3·32) | −0·10 (−0·17 to −0·03) | −0·19 (−0·29 to −0·09) | 0·09 (−0·04 to 0·21) |
| **MRS** | | | | |
| MRS VLFF | 2·13 (0·15 to 4·11) | 7·63 (6·10 to 9·17) | 10·56 (8·33 to 12·78) | −2·92 (−5·64 to −0·20) |

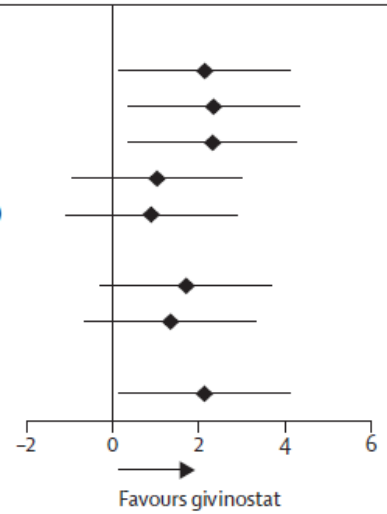



*Figure 2:* Forest plot of primary and secondary endpoints at week 72

Ref: Mercuri, E., Vilchez, J. J., Boespflug-Tanguy, O., Zaidman, C. M., Mah, J. K., Goemans, N., Müller-Felber, W., Niks, E. H., Schara-Schmidt, U., Bertini, E., Comi, G. P., Mathews, K. D., Servais, L., Vandenborne, K., Johannsen, J., Messina, S., Spinty, S., McAdam, L., Selby, K., Byrne, B., … EPIDYS Study Group (2024). Safety and efficacy of givinostat in boys with Duchenne muscular dystrophy (EPIDYS): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. *The Lancet. Neurology*, *23*(4), 393–403. https://doi.org/10.1016/S1474-4422(24)00036-X

# Use of External Evidence

| Strengths | Limitations |
| --- | --- |
| • Large, prospective datasets<br>• Standardized, longitudinal outcomes<br>• Imaging biomarkers well characterized | • Residual confounding<br>• Standard of care evolution over time<br>• Post-hoc propensity score matching concerns |

# Summary & Lessons Learned

Summary

Rigorously collected and shared NH data is accepted as confirmatory evidence and supportive evidence for regulatory approval

**Lessons Learned**

- Pre-specify NH integration
- Use of biomarkers such as MR FF for stratification
- Align trial endpoints with NH cohorts
- Data sharing de-risks drug development and gets us closer to new treatments
- Plan for continued and updated data collection

# Acknowledgements


## Thank you!!!

- Families and participants, CINRG and ImagingNMD teams, EPIDYS investigators

- Many thanks to Parent Project Muscular Dystrophy and the Duchenne Regulatory Science Consortium (D-RSC) members including: Binghamton University, Children's Hospital of Philadelphia, Children's National Health System, Children's National Heart Institute, Cincinnati Children's Hospital Medical Center, Hadassah Medical Center, Icahn School of Medicine at Mount Sinai, Indiana University School of Medicine, KTH-Royal Institute of Technology, Leiden University Medical Center, Nationwide Children's Hospital, Oregon Health & Science University, Paris Cite University, Stanford University, UH Rainbow Babies and Children's Hospital, UMass Memorial, University of Arizona, University of California, Davis, University of Florida, University of Leicester, UK, University of Messina, Italy, University of Oxford, Vanderbilt University Medical Center, CureDuchenne, Avidity Biosciences, Dyne Therapeutics, Edgewise Therapeutics, Entrada Therapeutics, Italfarmaco, NS Pharma, PepGen, REGENXBIO, Roche, Sarepta Therapeutics, Vertex, and Wave Life Sciences. With special thanks to Dr. Sarah Kim and her team at University of Florida, the Cooperative International Neuromuscular Research Group (CINRG) Investigators from the CINRG DMD Natural History Study (DNHS), and ImagingNMD Investigators.

FDA acknowledgement: Critical Path Institute is supported by the Food and Drug Administration (FDA) of the Department of Health and Human Services (HHS) and is 56% funded by the FDA/HHS, totaling $23,740,424, and 44% funded by non-government source(s), totaling $18,881,611. The contents are those of the author(s) and do not necessarily represent the official views of, nor an endorsement by, FDA/HHS or the U.S. Government.

CRITICAL PATH
INSTITUTE

Advancing Drug Development.
Improving Lives. Together.

c-path.org

# Advancing a Pipeline of Nucleic Acid Based Therapies for Cystic Fibrosis:

## External Control Strategy to Address a Diminishing Participant Pool

Nicole Mayer Hamblett, PhD

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

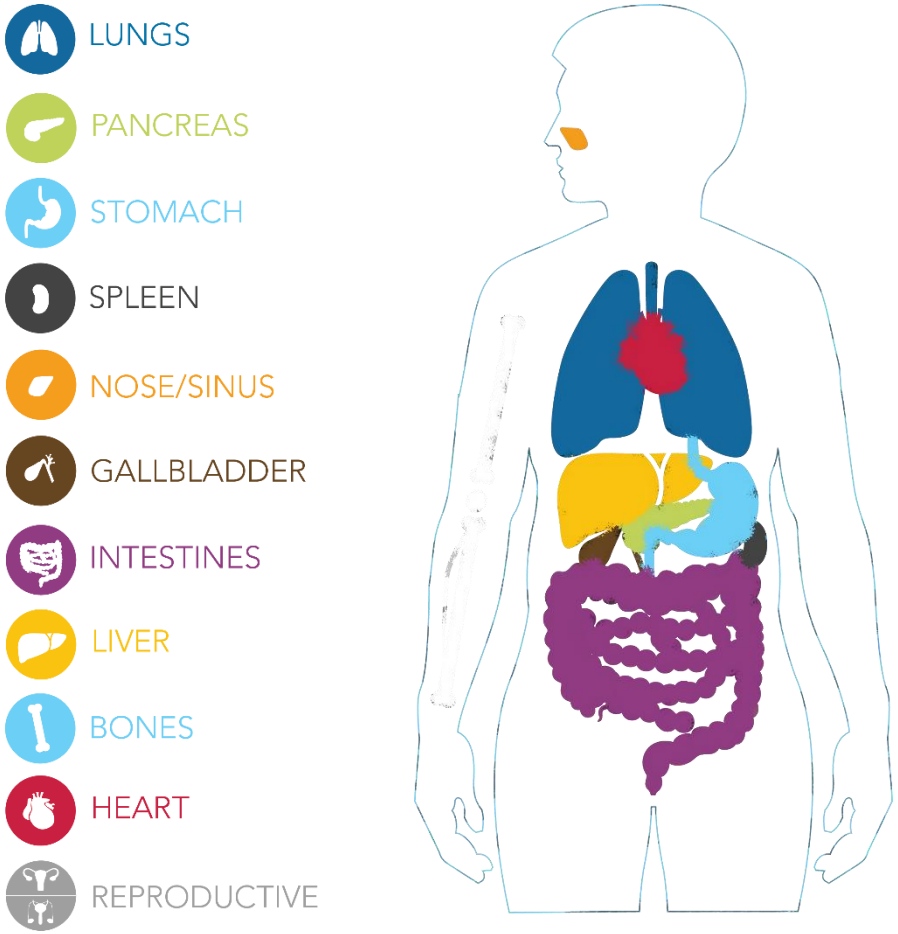
Professor, Pediatrics, Adjunct Professor, Biostatistics
University of Washington

CYSTIC FIBROSIS THERAPEUTICS DEVELOPMENT NETWORK

CYSTIC FIBROSIS FOUNDATION®

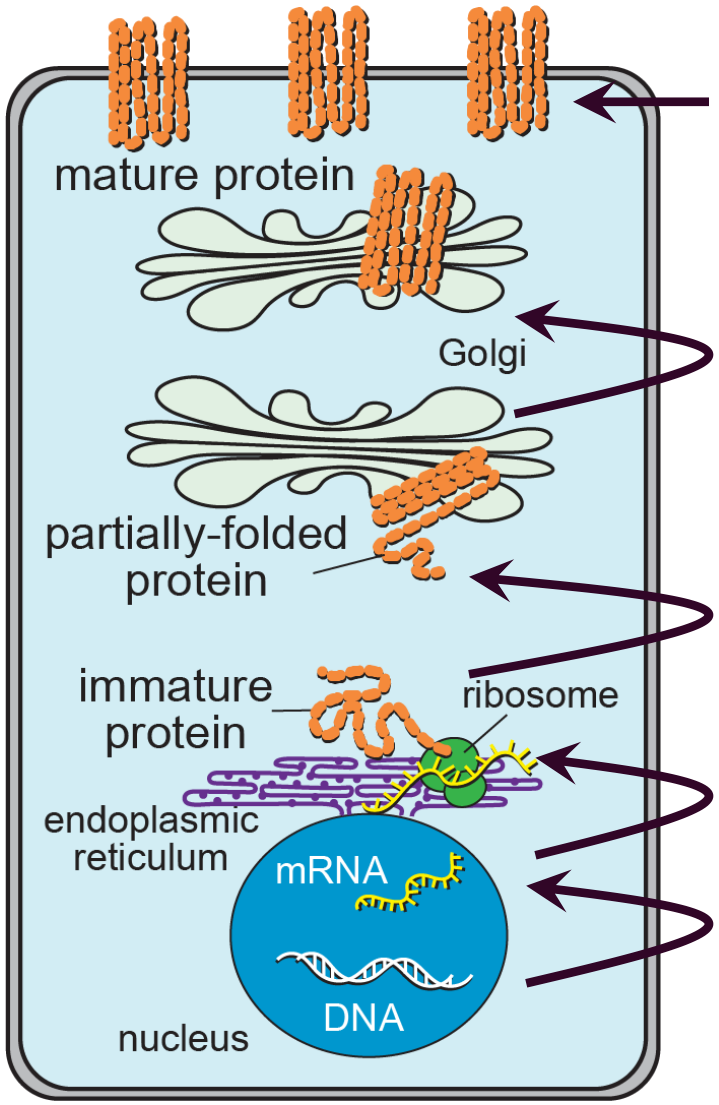
# Cystic fibrosis (CF)

- Life-shortening, multi-organ disease caused by variants in the CFTR gene
- ~40K people living with CF in the US
- Recent success with therapies targeting the underlying cause of CF by improving defective CFTR protein function
- CFTR modulators have dramatically improved clinical outcomes for many *but not all* people with CF




2021 Annual Data Report. Bethesda, Maryland. ©2022 CFF
*Cromwell et. al. Journal of Cystic Fibrosis 22 (2023) 436–442

# ~10% with CF are Not Candidates for CFTR Modulators




function

transport

processing

translation

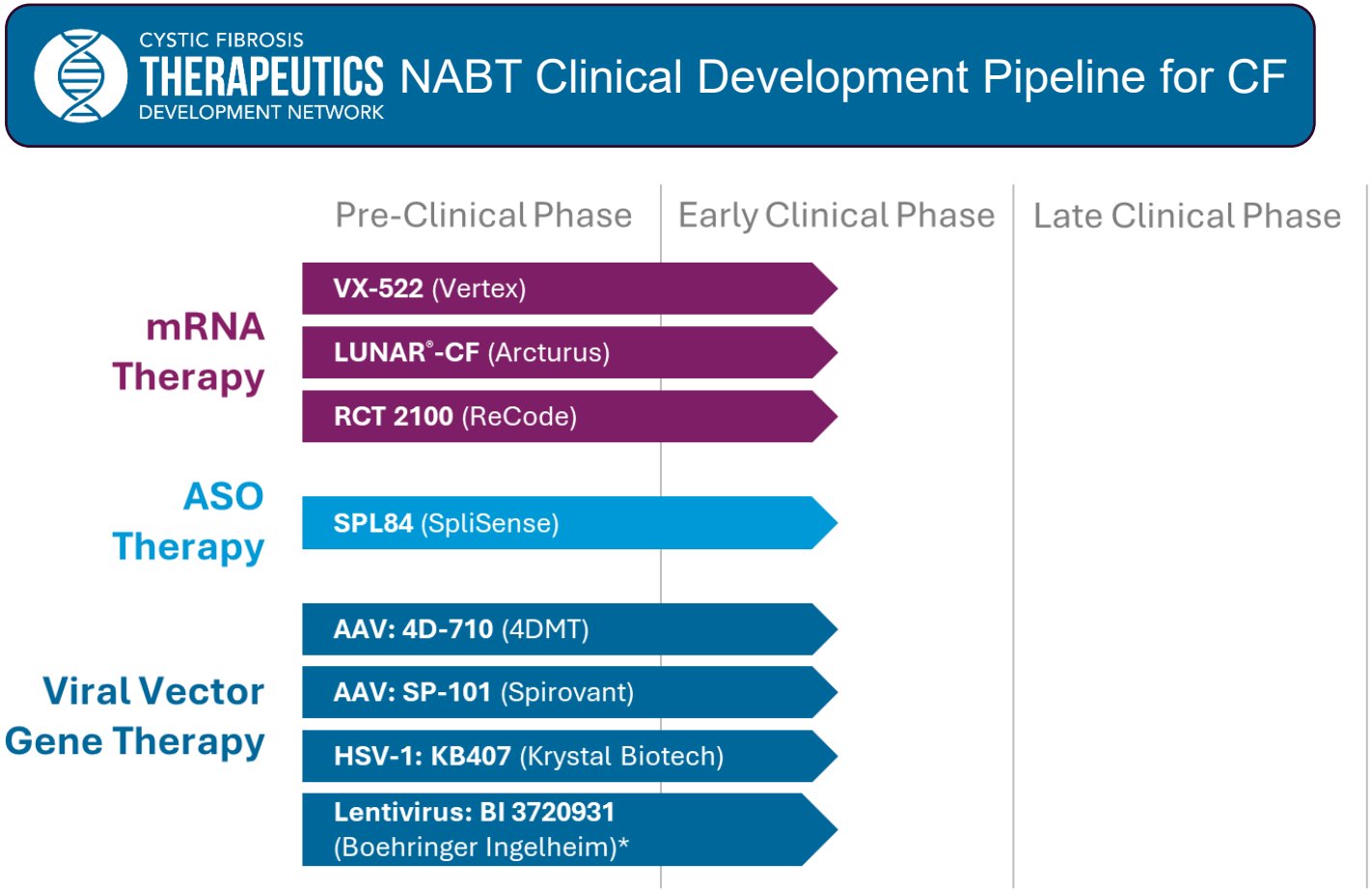
transcription

- ~90% of people with CF carry at least one CFTR variant that produces a dysfunctional protein for which modulators could restore and/or increase function

- ~10% of people with CF are not candidates for modulators
- Some have variants that may not even produce CFTR protein
- Will require **nucleic acid-based therapies (NABTs)** to produce and/or provide CFTR function

*Welsh, MJ and Smith, AE, Cell 1993;73:1251-1254; Slide Adapted from B. Ramsey PAS April 2025*

# NABT Pipeline for those who are Not Candidates for CFTR Modulators




- NABTs include mRNA therapies, ASOs, and viral-vector gene therapies
  - CFTR gene editing approaches in *pre-clinical* development
- CF NABTs are inhaled therapies
  - Face complex delivery obstacles to the CF lung
  - Require varying re-dosing frequencies (for some therapies due to lung cell turnover)

➢ **Multiple therapeutic "shots on goal" needed**

https://apps.cff.org/trials/pipeline/ for current;
*Active in CF but not currently in CFF pipeline

# NABT Pipeline for those who are Not Candidates for CFTR Modulators

CYSTIC FIBROSIS THERAPEUTICS DEVELOPMENT NETWORK NABT Clinical Development Pipeline for CF

| | Pre-Clinical Phase | Early Clinical Phase | Late Clinical Phase |
|---|---|---|---|
| mRNA Therapy | **VX-522** (Vertex) | | |
| | **LUNAR®-CF** (Arcturus) | | |
| | **RCT 2100** (ReCode) | | |
| ASO Therapy | **SPL84** (SpliSense) | | |
| Viral Vector Gene Therapy | **AAV: 4D-710** (4DMT) | | |
| | **AAV: SP-101** (Spirovant) | | |
| | **HSV-1: KB407** (Krystal Biotech) | | |
| | **Lentivirus: BI 3720931** (Boehringer Ingelheim)* | | |

**~840**

**adults with CF in US ineligible for modulators**

***& meet key eligibility criteria***

https://apps.cff.org/trials/pipeline/ for current;
*Active in CF but not currently in CFF pipeline

Mayer-Hamblett *Lancet Resp* 2025

# Unique Risks of a Diminishing NABT Participant Pool

- Individuals **may have limited NABT trial opportunities over their lifetime**
  - While inhaled CF NABTs are not “one shot” therapies, there are are concerns for re- or cross-product exposure particularly when moving w/i and across viral-vector based therapies

- Individuals in genetic therapy trials are required to participate in **long-term safety studies (up to 15 years)**
  - Regardless of therapeutic benefit and study phase
  - Will complicate feasibility of concurrent participation in alternative investigational trials from competing sponsors

Mayer-Hamblett et. al. Maximizing Opportunity for Therapeutic Success: Sequential Participation in CF NABT Trials. *Lancet Resp* July 2025

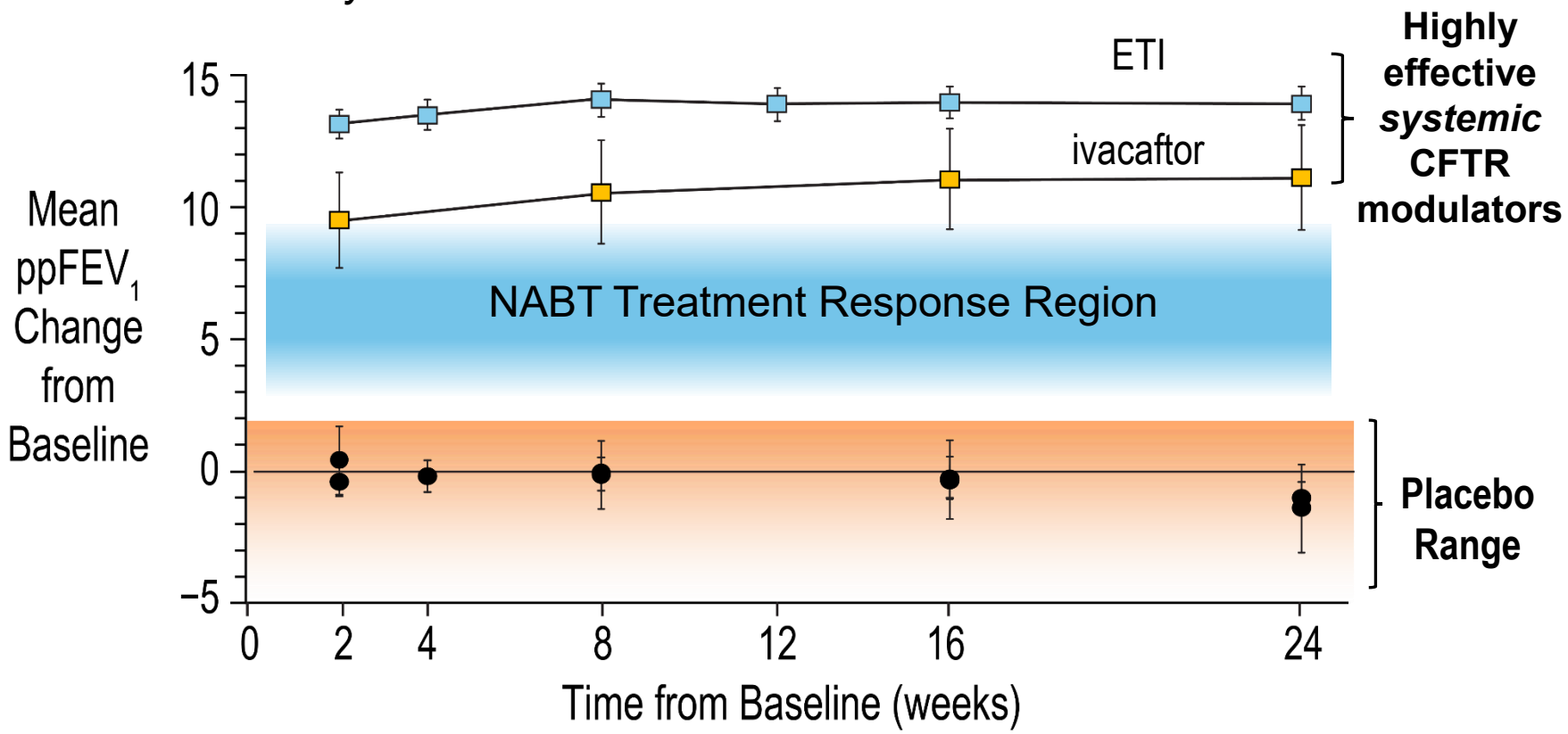
FDA

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

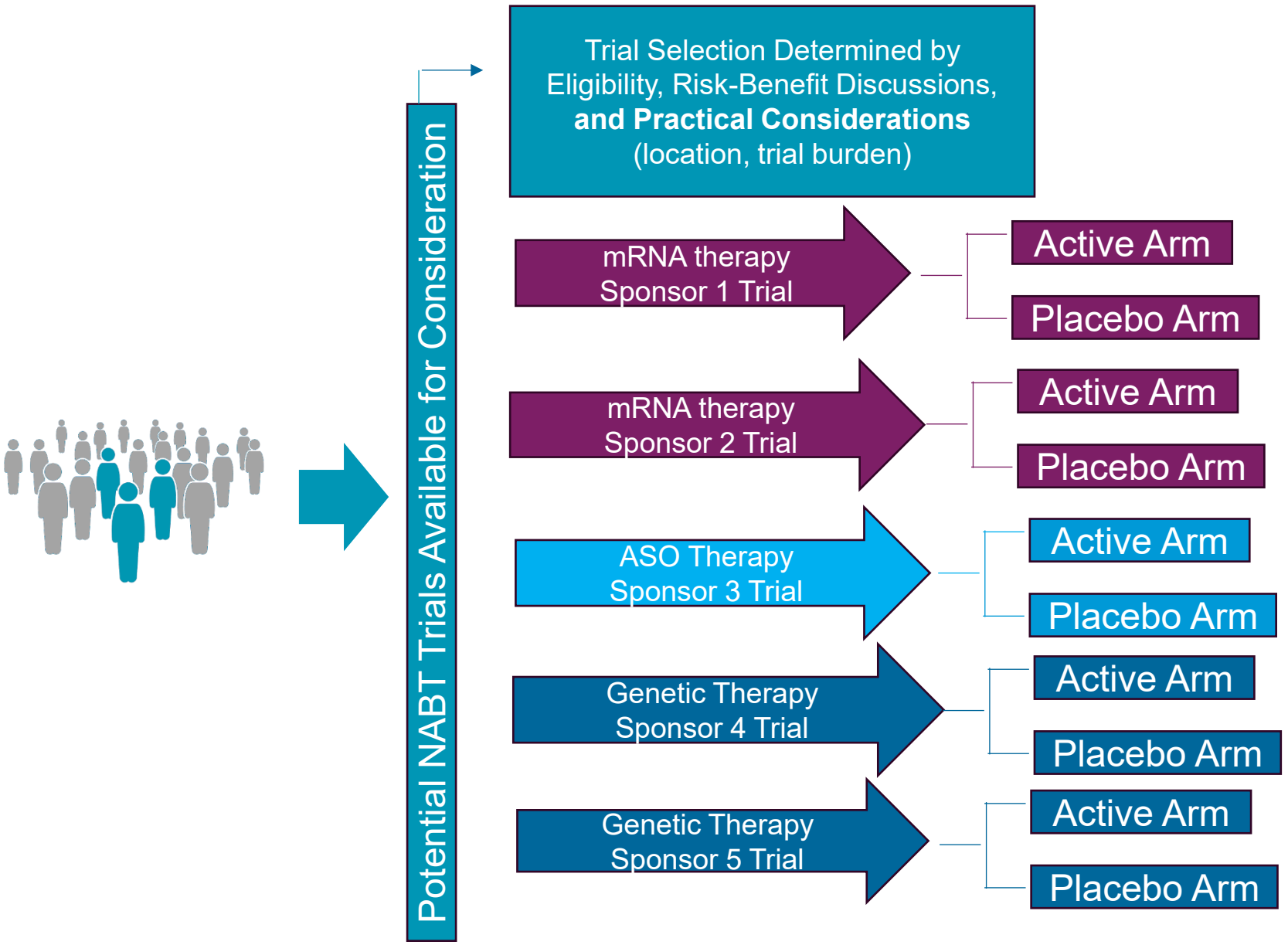
# Advancing the Pipeline will Necessitate Innovative Approaches to Streamline Trial Sizes

- CF NABT development is an excellent opportunity for use of external controls
- We hypothesize an effective NABT will produce a **robust and meaningful effect** on lung function improvement
  - *Above that expected based on natural variability*

**_Inhaled_ NABT treatment effects will likely be attenuated in comparison to _systemic_ CFTR therapies, but nonetheless clinically impactful**



# External Controls to Advance the NABT Pipeline



# External Controls to Advance the NABT Pipeline

Potential NABT Trials Available for Consideration

Trial Selection Determined by Eligibility, Risk-Benefit Discussions, **and Practical Considerations** (location, trial burden)

- mRNA therapy Sponsor 1 Trial
  - Active Arm
  - Placebo Arm
- mRNA therapy Sponsor 2 Trial
  - Active Arm
  - Placebo Arm
- ASO Therapy Sponsor 3 Trial
  - Active Arm
  - Placebo Arm
- Genetic Therapy Sponsor 4 Trial
  - Active Arm
  - Placebo Arm
- Genetic Therapy Sponsor 5 Trial
  - Active Arm
  - Placebo Arm

**External Control Repository**

CYSTIC FIBROSIS FOUNDATION®

CYSTIC FIBROSIS THERAPEUTICS DEVELOPMENT NETWORK

CRITICAL PATH INSTITUTE

RDCA-DAP® Rare Disease Cures Accelerator Data and Analytics Platform

# CFF-TDN Investment in an External Control Data Repository

**RWD: Natural History Data From the CF Patient Registry**


**Archived Clinical Trial Data and Contributing Placebo Data**

REACH CF
One discovery at a time.

**"Fit for purpose" prospective study to collect control data**

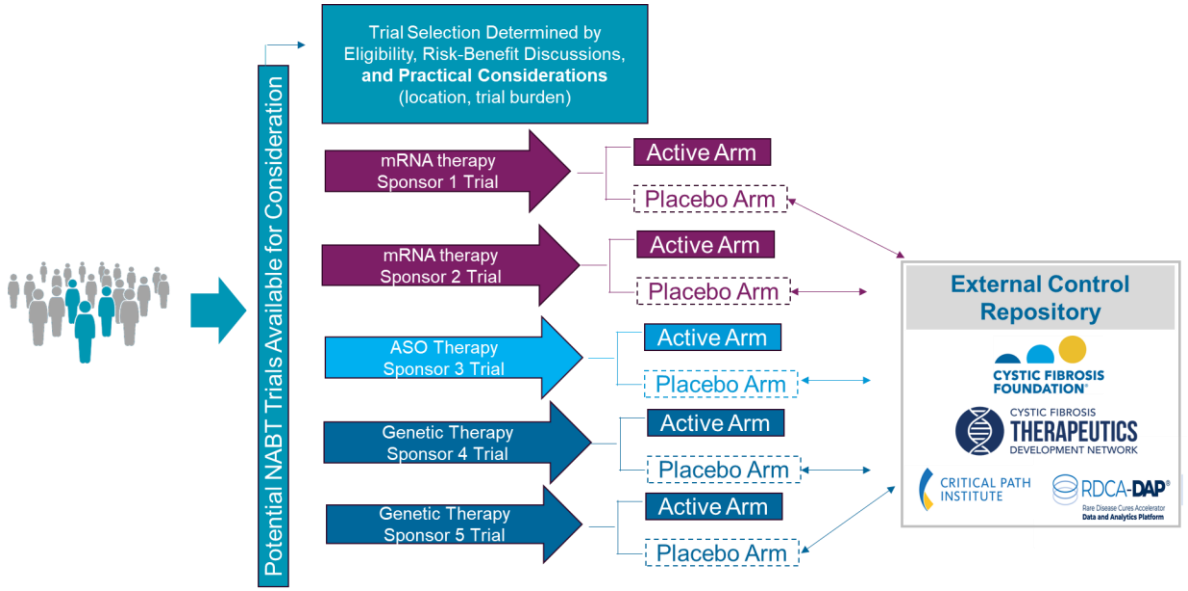
-Standardized outcomes and time points aligning w/ the NABT trials
-Comparative safety in addition to efficacy data
-Remote & onsite monitoring, use of regulatory compliant data systems
-Conducted in the same trial network as the NABT trials

COMMUNITY VOICE
CYSTIC FIBROSIS FOUNDATION

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

reachcfstudy.com; PI: D. Polineni, WUSTL

# A “Deconstructed” Master Protocol Approach to Advance the Pipeline




Individual sponsors will run separate NABT trials in parallel, but utilize a shared control resource

## Advantages

- Solves *our* most critical issue of decreasing trial sizes (rather than operational efficiency), enabling more shots on goal
- Does not require an exceptionally complex (*particularly for NABTs*) traditional master protocol negotiated across competing sponsors

## Challenges to Address

- Must mitigate multiple concerns outlined in FDA External Control Guidance (2023)
  - ~~Outcome validity, Data quality, Lack of concurrence~~
  - Selection bias, Unmeasured confounding

REACH CF
One discovery at a time.

# CFF-TDN Investment in External Control Data *Methods*

Identify efficient and robust methods incorporating external controls to estimate and test for treatment effects in NABT trials

CYSTIC FIBROSIS THERAPEUTICS DEVELOPMENT NETWORK

telperian

Key Simulation Factors (Hybrid Controlled Trial- HCT)

Trial size
30-40 active vs. 8-10 control

Rx effect size
$ppFEV_1$ Δ 3-10%

Unmeasured confounding vs. none

Statistical Methods:

- Multivariable commensurate priors
- Bayesian additive regression trees (BART)
- Inverse probability weighting in a CP model
- Propensity score stratified meta analytic predictive prior
- Full borrowing using augmented calibration weighting (FB-ACW)
- Selective borrowing using ACW (SB-ACW)

Bayesian and frequentist methods to test for evidence of **average treatment effects**

+ Methods extending randomization inference framework to HCTs to test the sharp null hypothesis of **no treatment effect**

Zhu et.al. (2025). Enhancing statistical validity and power in hybrid controlled trials: a randomization inference approach with conformal selective borrowing. *The 41st (ICML) International Conference on Machine Learning*. [arxiv]

# CFF-TDN Investment in External Control Data *Methods*

Identify efficient and robust methods incorporating external controls to estimate and test for treatment effects in NABT trials

CYSTIC FIBROSIS THERAPEUTICS DEVELOPMENT NETWORK

telperian

## Key Simulation Factors (Hybrid Controlled Trial- HCT)

Trial size
30-40 active vs. 8-10 control

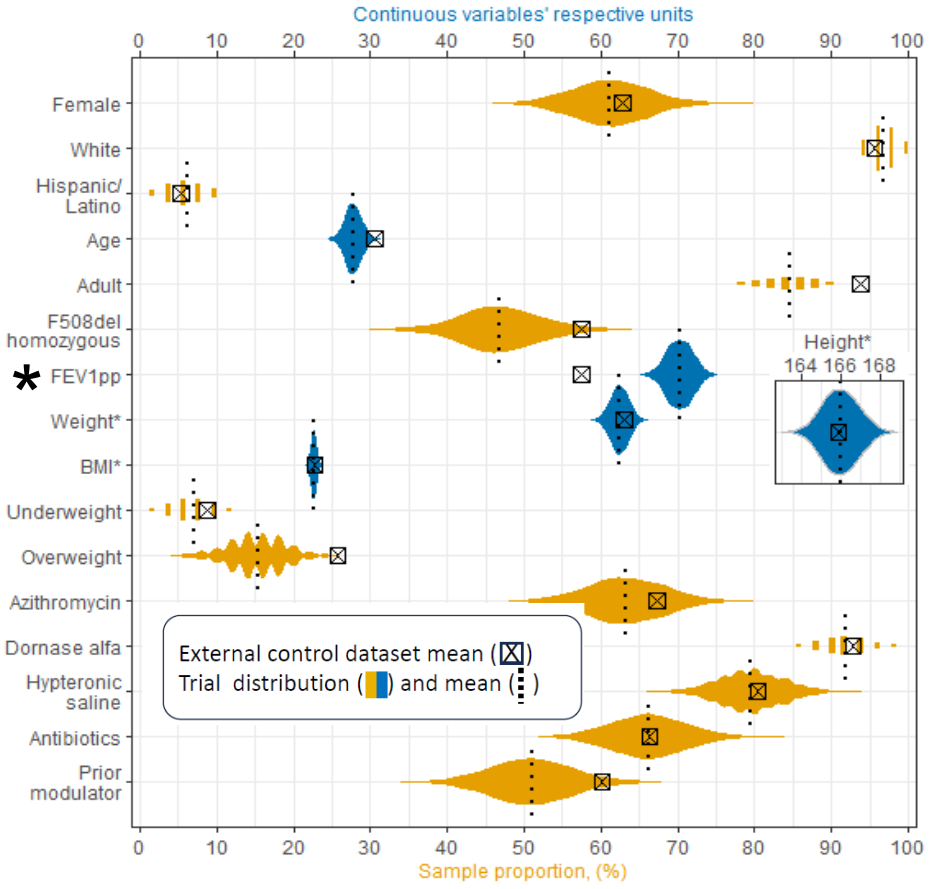
Rx effect size
ppFEV$_1$ Δ 3-10%

Unmeasured confounding vs. none

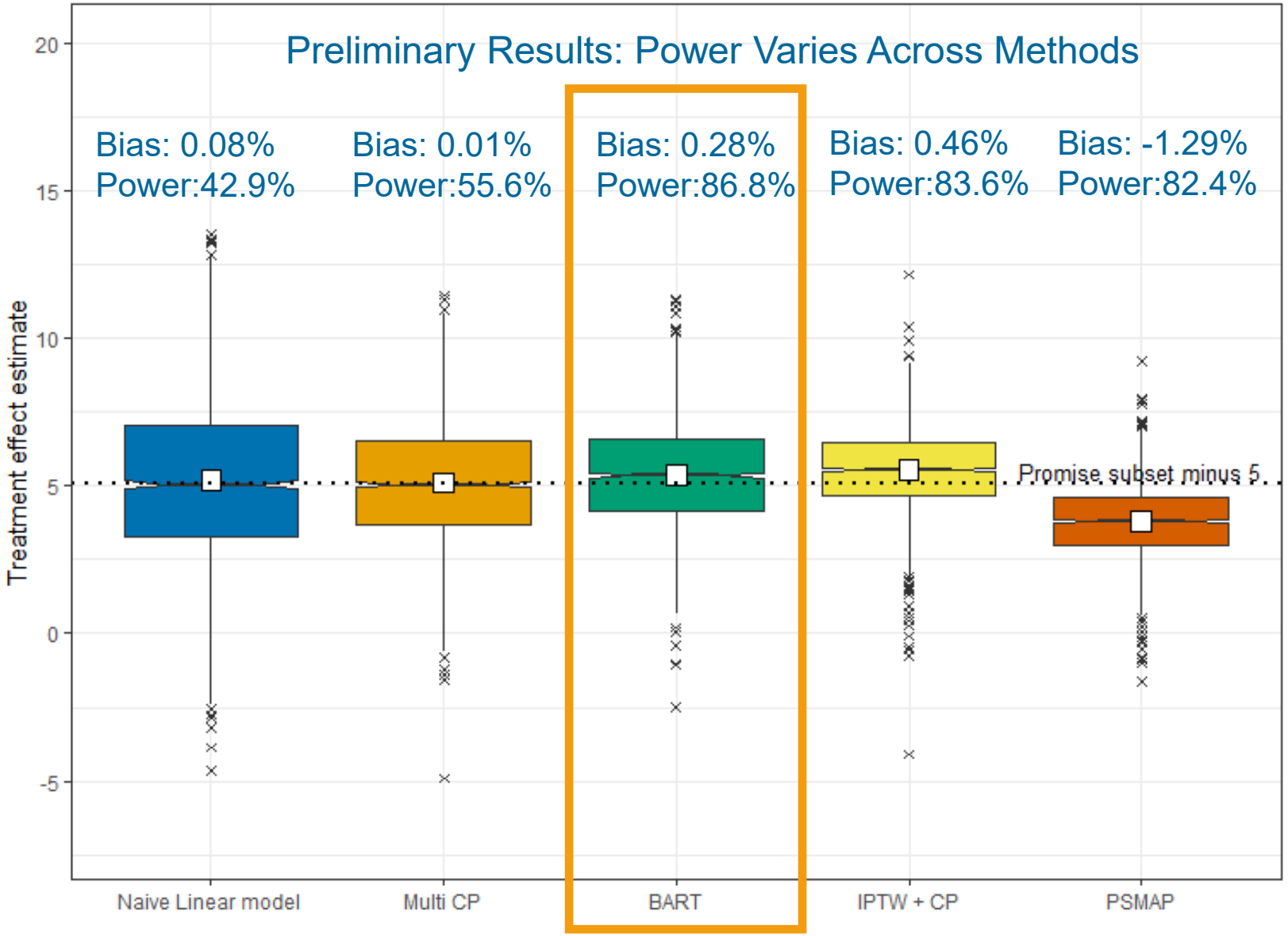
Statistical Methods:

- Multivariable commensurate priors
- Bayesian additive regression trees (BART)
- Inverse probability weighting in a CP model
- Propensity score stratified meta analytic predictive prior
- Full borrowing using augmented calibration weighting (FB-ACW)
- Selective borrowing using ACW (SB-ACW)

Comparison of baseline characteristics between external controls and simulated trial datasets



# Minimal Bias using External Controls in a “Small” CF HCT Trial
# NABT Treatment Effect Assumed = 5%




Warden, Magaret, Heltshe Unpublished

# External Controls Can Maximize Therapeutic Shots on Goal for a Diminishing Participant Pool



- A sponsor agnostic strategy to address an urgent unmet need
  - Shared control data repository, including “fit for purpose” controls, enables multiple sponsors to efficiently progress in parallel
  - Independent methods evaluation promotes the consistent use of robust methods across the pipeline

- Collaboration with the FDA Rare Disease Innovation Hub is critical to advance this strategy in a sponsor agnostic fashion

# Session 3: External Control Options

*Moderator:*

- **Rachele Hendricks-Sturrup**, Duke-Margolis Institute for Health Policy

*Presentations:*

- **Ramona Belfiore-Oshan,** Critical Path Institute (C-Path)
- **Nicole Mayer Hamblett**, Cystic Fibrosis Therapeutics Development Network

*Panelists:*

- **Najat Bouchkouj**, CBER, U.S. Food and Drug Administration
- **Scott Demarest**, Children's Hospital Colorado
- **Tracey Sikora**, National Organization for Rare Disorders (NORD)
- **Arup Sinha**, CDER, U.S. Food and Drug Administration

Join at
slido.com
#RISE

# Moderated Discussion and Q&A

**Moderator:** Rachele Hendricks-Sturrup, Duke-Margolis Institute for Health Policy

# BREAK

## Our Program Will Resume at 3:15 PM ET

Scan to Register


## Upcoming Duke-Margolis Hybrid Public Workshop

**September 23, 2025|9:30 – 4:00 PM ET**

Visit healthpolicy.duke.edu/events

# Session 4: Where do we go from here?

3:15 – 3:55pm ET

**Moderator:** Steve Berman, Biotechnology Innovation Organization (BIO)

# Session 4: Where do we go from here?

*Moderator:*

- **Steve Berman**, Biotechnology Innovation Organization (BIO)

*Panelists:*

- **Samiah Al-Zaidy**, Alexion
- **Elizabeth Berry-Kravis**, Rush University
- **Mary Dwight**, Cystic Fibrosis Foundation
- **Annie Kennedy**, EveryLife Foundation for Rare Diseases
- **Vijay Kumar**, CBER, U.S. Food and Drug Administration
- **Mark Levenson**, CDER, U.S. Food and Drug Administration

Duke
MARGOLIS INSTITUTE for Health Policy

Join at
slido.com
#RISE

# Moderated Discussion and Q&A

**Moderator:** Steve Berman, Biotechnology Innovation Organization (BIO)

# Concluding Remarks

**Gerrit Hamre**, Duke-Margolis Institute for Health Policy

# Adjournment

## On The RISE: Controls in Rare Disease Clinical Trials for Small and Diminishing Populations

September 3, 2025 | 9:30 am – 4:00 pm ET

Duke | MARGOLIS INSTITUTE for Health Policy

# Thank You!

## Contact Us

**healthpolicy.duke.edu**

Subscribe to our monthly newsletter at dukemargolis@duke.edu

1201 Pennsylvania Avenue, NW,
Suite 500 • Washington, DC 20004

DC office: 202-621-2800
Durham office: 919-419-2504

## Follow Us

DukeMargolis

@dukemargolis

@DukeMargolis

Duke Margolis

Duke-Margolis Institute For Health Policy

Duke | MARGOLIS INSTITUTE *for* Health Policy