

Precision medicine approaches to asthma: Lessons from the PrecISE Trial

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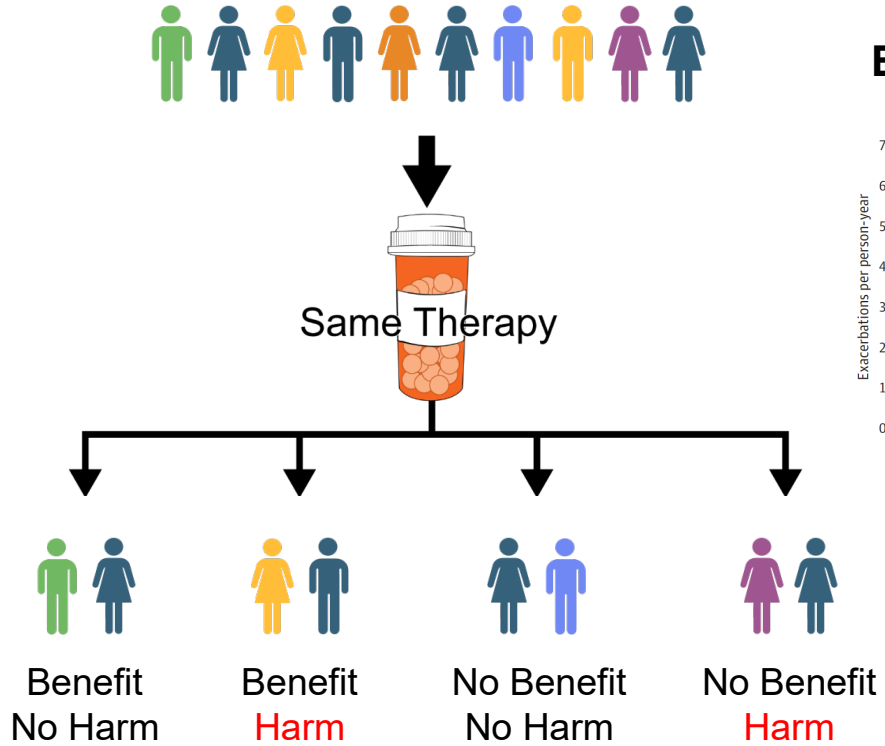
University of Rochester Medical Center

Rochester, NY

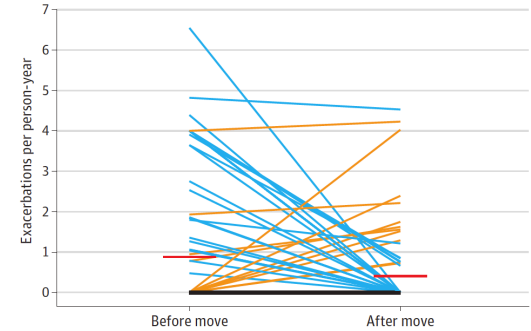
Disclosure to Learners

- Relevant Financial Relationships within the last 24 months:
 - Dr. Georas reports consulting agreements with AstraZeneca

Without Precision Medicine



Beware: the tyranny of the mean!



With Precision Medicine: 2026

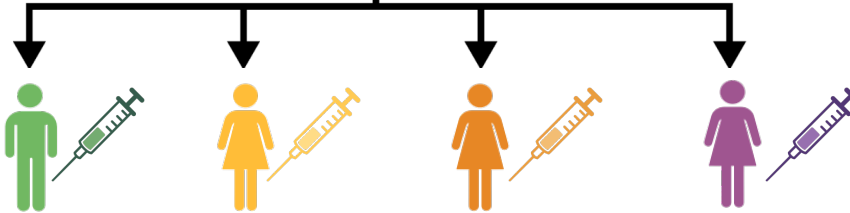


Predictive Biomarkers

Blood eosinophil count (Eos)

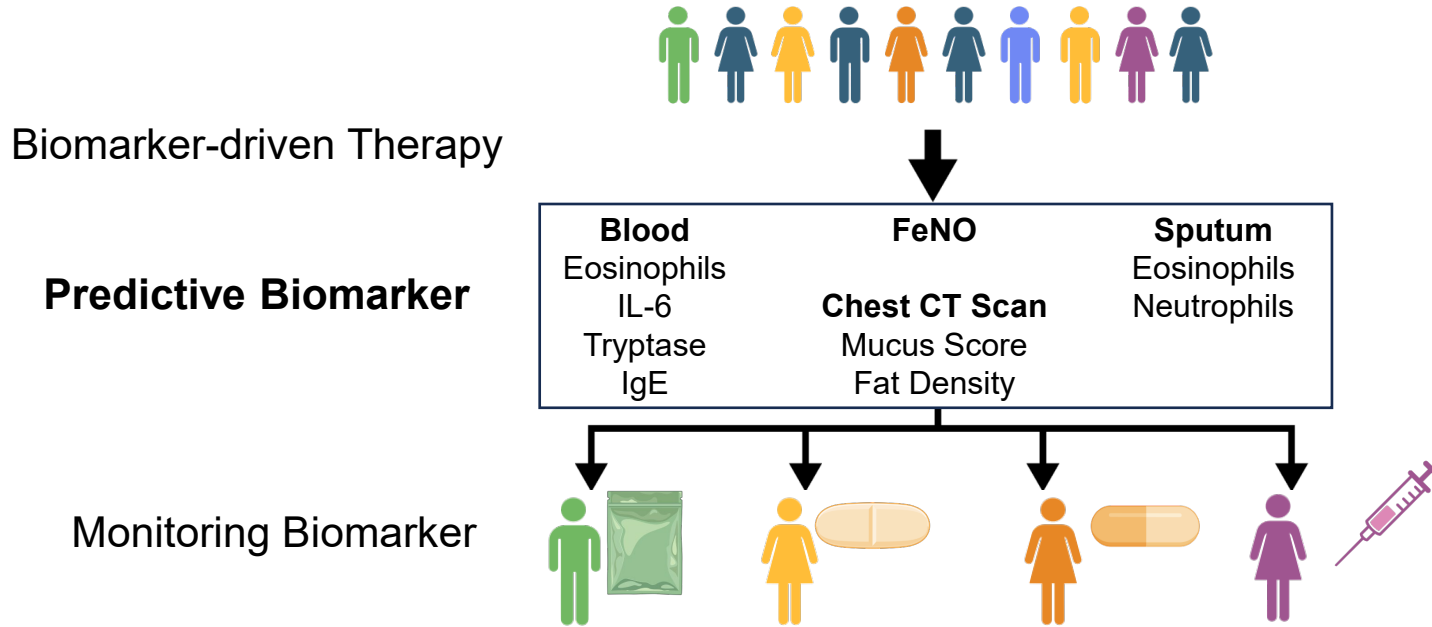
Fractional exhaled nitric oxide (FeNO)

Type 2 asthma biologics



Benefit
No Harm

The Promise of Precision Medicine in Asthma

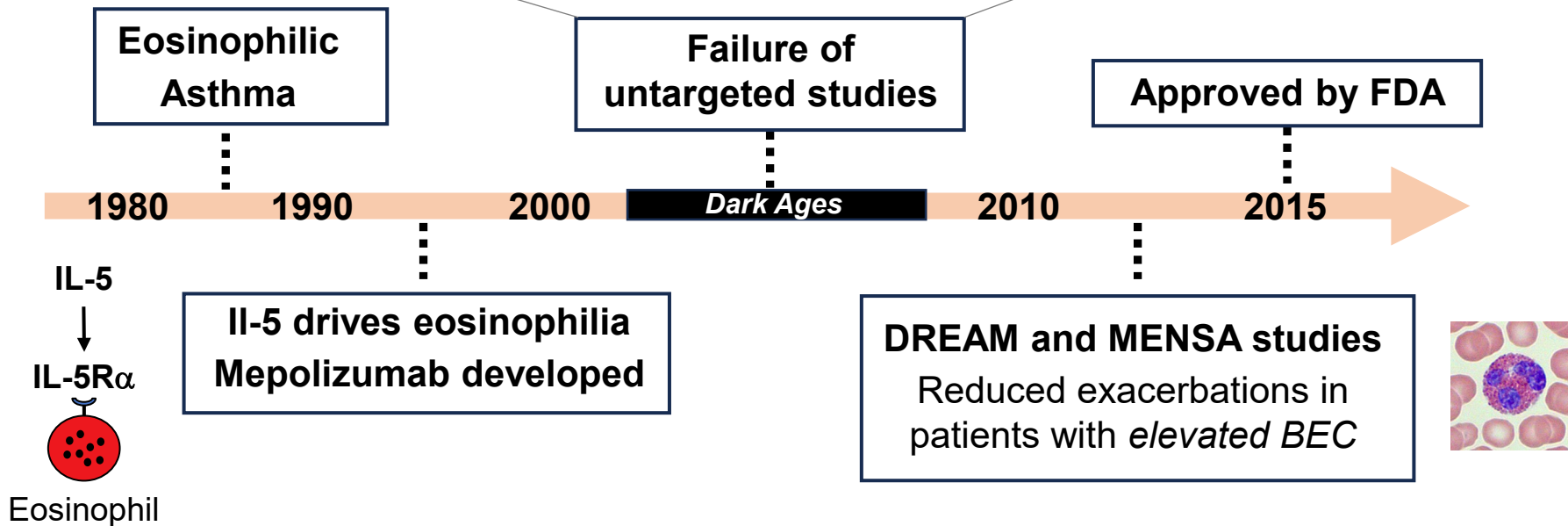


Lessons from mepolizumab: target the right subgroup!

Eosinophil's Role Remains Uncertain as Anti-Interleukin-5 only Partially Depletes Numbers in Asthmatic Airway

Patrick T. Flood-Page,* Andrew N. Menzies-Gow,* A. Barry Kay, and Douglas S. Robinson

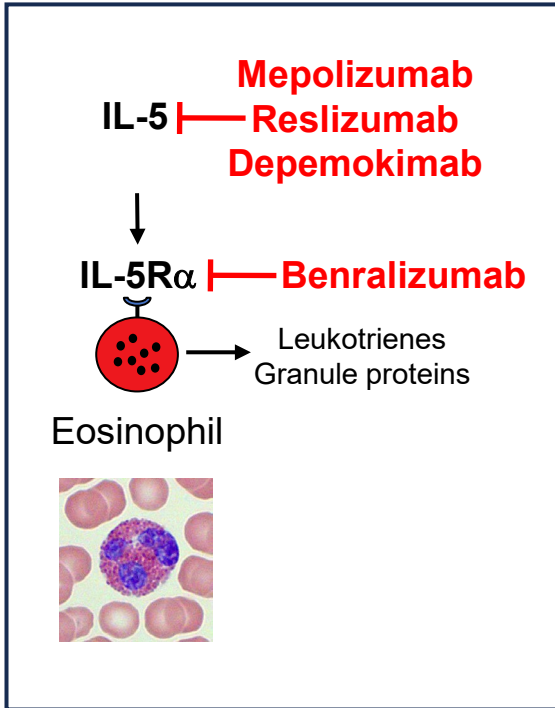
Am J Resp Crit Care Med 2003



Pavord et al, *Lancet* 2012

Ortega et al, *N Eng J Med* 2014

Blood eosinophils and IL-5 antagonists



Blood eosinophils in severe asthma:

- Predict exacerbations and poor control
- Predict response to steroids
- Predict response to T2 biologics

Some problems remain:

- Blood eosinophils \neq Tissue eosinophils
- Eosinophil count \neq eosinophil activation
- Increase in blood eosinophils is associated with *better* FEV1 response to dupilumab
- Effect of steroid treatment impacts cut-offs
- What is best: $>150/\mu\text{l}$, $>300/\mu\text{l}$, or ...?

Precision Medicine in Asthma: room for improvement

Blood eosinophils and FeNO are indirect markers of tissue inflammation

Need to take airway structural defects into account (not just immune dysregulation)

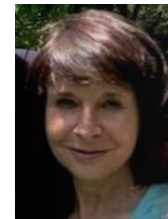
Although type 2 biologics have improved severe asthma clinical care, they are not disease modifying ... need to strive for disease remission

Non-type 2 pathways are increasingly common and poorly understood

- Epithelial metabolism and barrier defects
- Mast-cell driven pathways
- Systemic inflammatory pathways
- Obesity associated asthma

Precision Interventions for Severe and/or Exacerbation Prone Asthma (PrecISE)

- Biomarker-driven precision medicine study funded by the NHLBI (2018-2025)
- Interventions inspired by mechanistic asthma research
- Key principles and objectives:



Patricia Noel



Jim Kiley

Innovate trial design

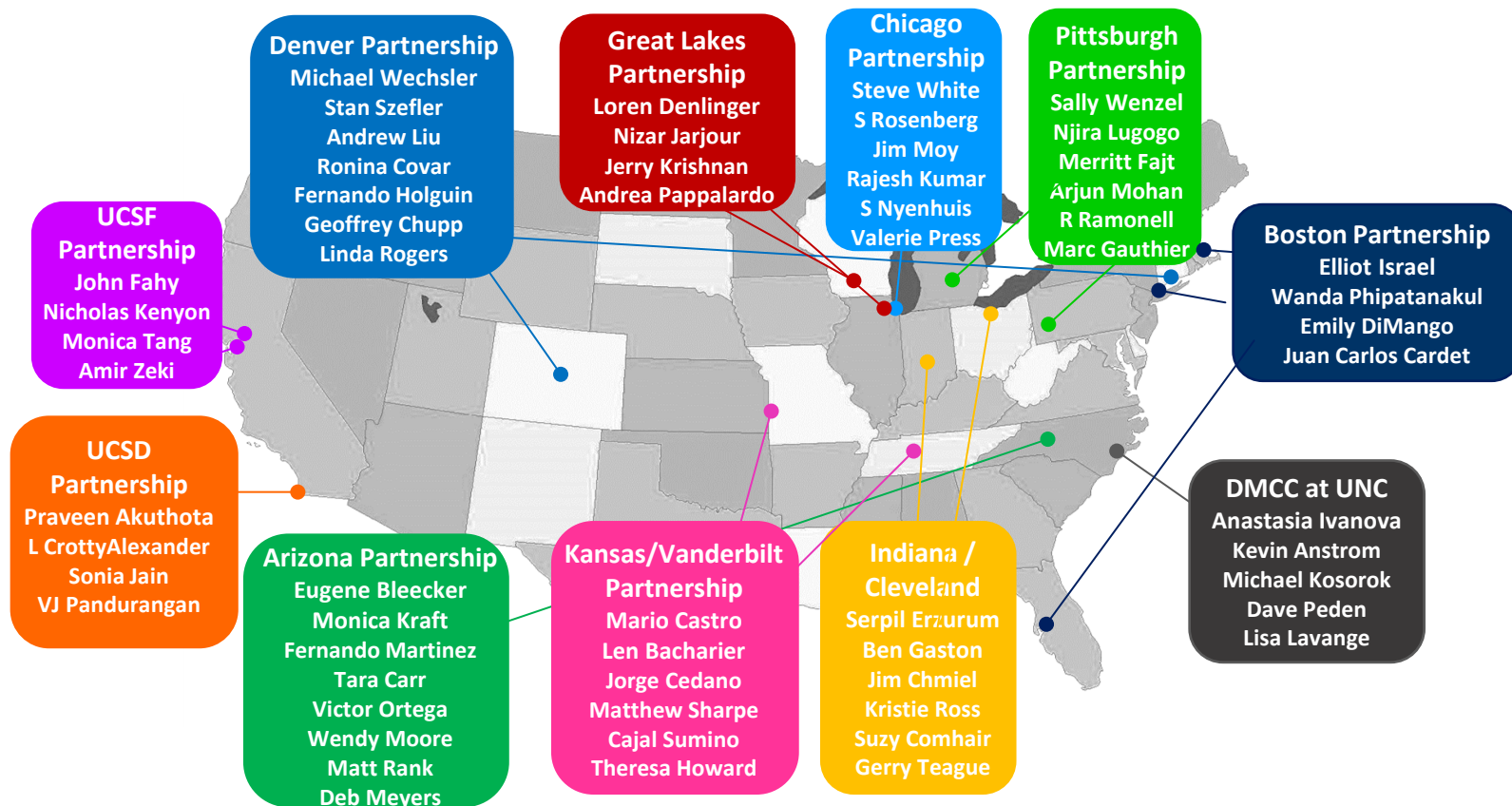
Use predictive and monitoring biomarkers

**Platform Trial with Master Protocol
Biomarker-driven Adaptive Enrichment
with Interim Futility Analyses**

Innovate interventions

**Five interventions
3 first in asthma**

PrecISE Network



SC Chairs: Steve Georas (U Rochester), Rosalind Wright (Mt. Sinai)

PrecISE Protocol: Initial Design

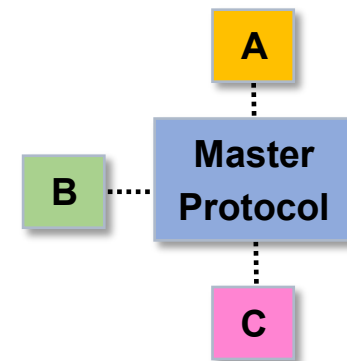
- Platform trial with Master Protocol
- Cross-over design with biomarker-driven randomizations
 - 16 week treatment, 8 week washout
- Chance to demonstrate efficacy on **any one of three outcomes:**

FEV₁
(percent predicted,
pre-albuterol)

ACQ-6

**CompEx
events**

Severe exacerbations or acute worsening
events based on symptoms, rescue
medication use, and peak expiratory flow
(CompEx: Fuhlbrigge et al, 2017)



PrecISE Design and Operations

Ivanova et al, *J Biopharm Stat*, 2020

Israel et al, *J All Clin Immunol*, 2021

Georas et al, *J All Clin Immunol*, 2021

Inclusion

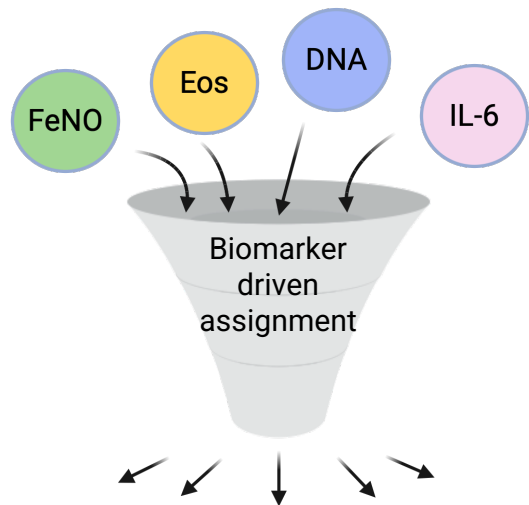
Age \geq 12 years
MBR > 12% or positive MCH
 \geq Medium dose ICS + 2nd controller
Meet ERS/ATS criteria

Exclusion

COPD
Prednisone > 10 mg/day
Smoking history
Additional safety criteria to mitigate risk while supporting recruitment

Uniform single consent

Digital technology



Biomarkers

FeNO = exhaled nitric oxide (ppb)

Eos = blood eosinophils (cells/ μ l)

DNA = GSNOR genotype

IL-6 = plasma interleukin-6 (pg/mL)

FeNO \geq 15



Medium Chain Triglycerides

Eos \geq 300



Broncho-Vaxom

Eos < 300



Imatinib

Genotype+



Cavosonstat

IL-6 > 3.1



Clazakizumab

**First
in
asthma**

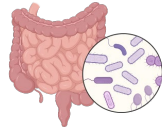
Medium Chain Triglycerides

Mitochondrial metabolism
Biomarker: FeNO \geq 15 ppb
Partner: Vitaflo/Nestle
WG Chair: S. Erzurum

Mitochondrial
Metabolism



Immune
Modulation



Broncho-Vaxom

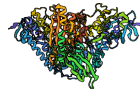
Immune modulation
Biomarker: Eos \geq 300/ μ l
Partner: OM Pharma
WG Chair: F. Martinez

First in asthma

Cavosonstat

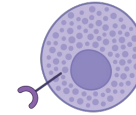
S-nitrosoglutathione reductase
Biomarker: GSNOR SNP
Partner: Laurel Therapeutics
WG Chair: B. Gaston

S-Nitrosothiols



Imatinib

Mast cell c-Kit tyrosine kinase
Biomarker: Eos $<$ 300/ μ l
Partner: Sun Pharma
WG Chair: E. Israel



Mast Cell c-Kit

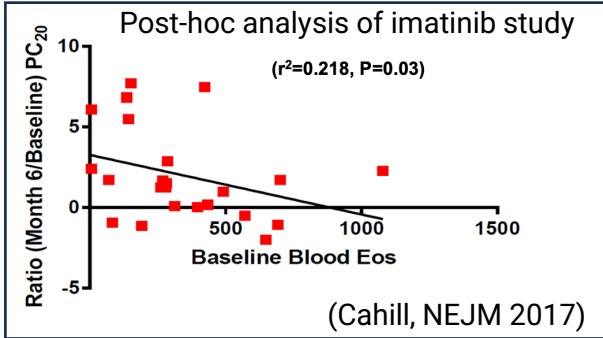
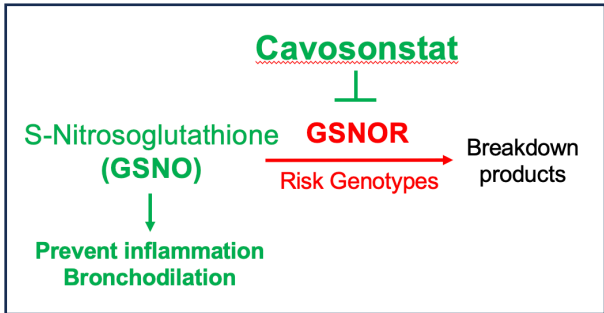
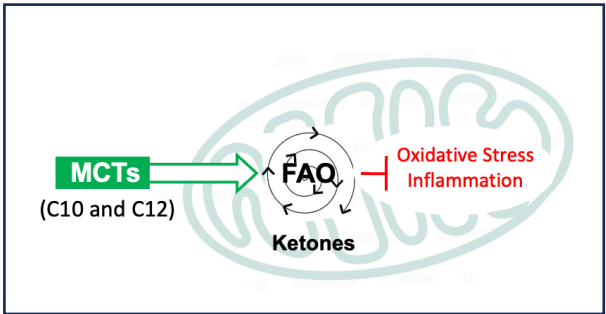


Systemic
Inflammation

Clazakizumab

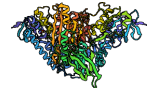
Anti-IL-6
Biomarker: IL-6 $>$ 3.1 pg/ml
Partner: CSL Behring
WG Chair: J. Fahy

**First
In
asthma**

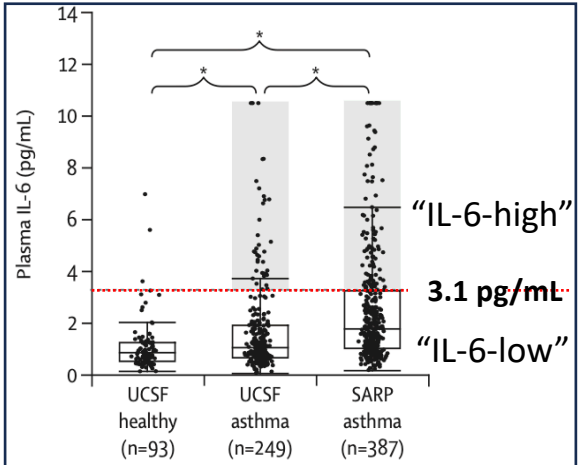
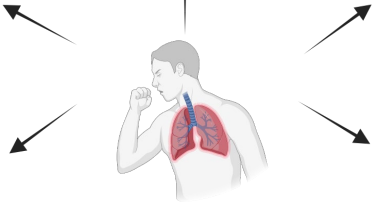
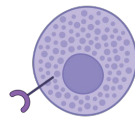


S-Nitrosothiols

Mitochondrial Metabolism

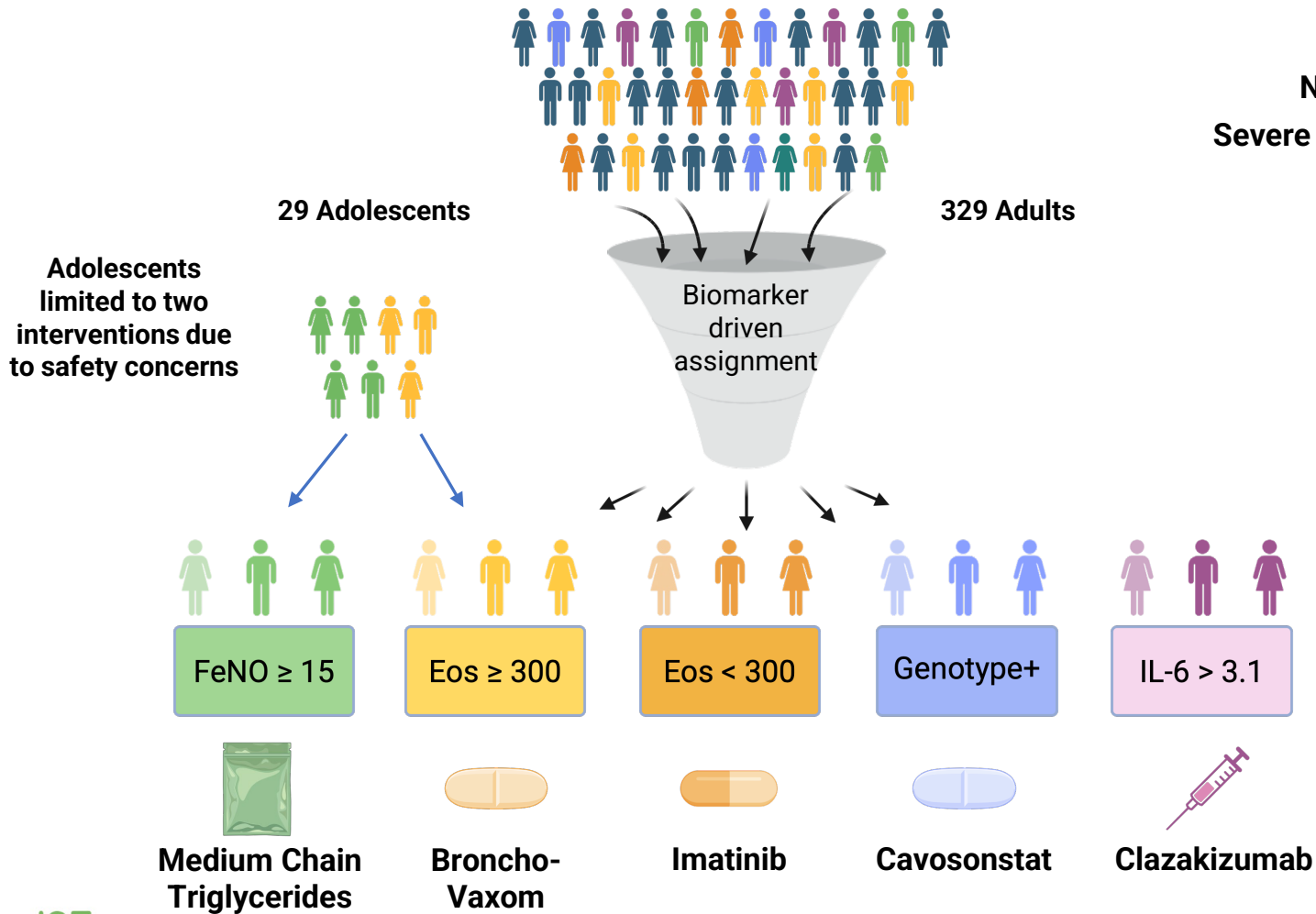


Mast Cell c-Kit



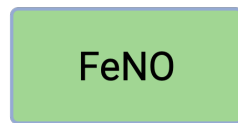
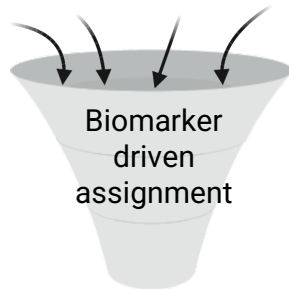
(Peters, Lancet Resp Med 2016)

N=358
Severe Asthmatics



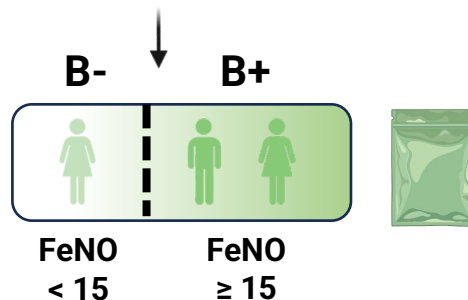
Because of uncertainty about cut-off values, Biomarker Positive (B+) and Biomarker Negative (B-) included in all interventions

Oversample B+, and adjust after interim analyses

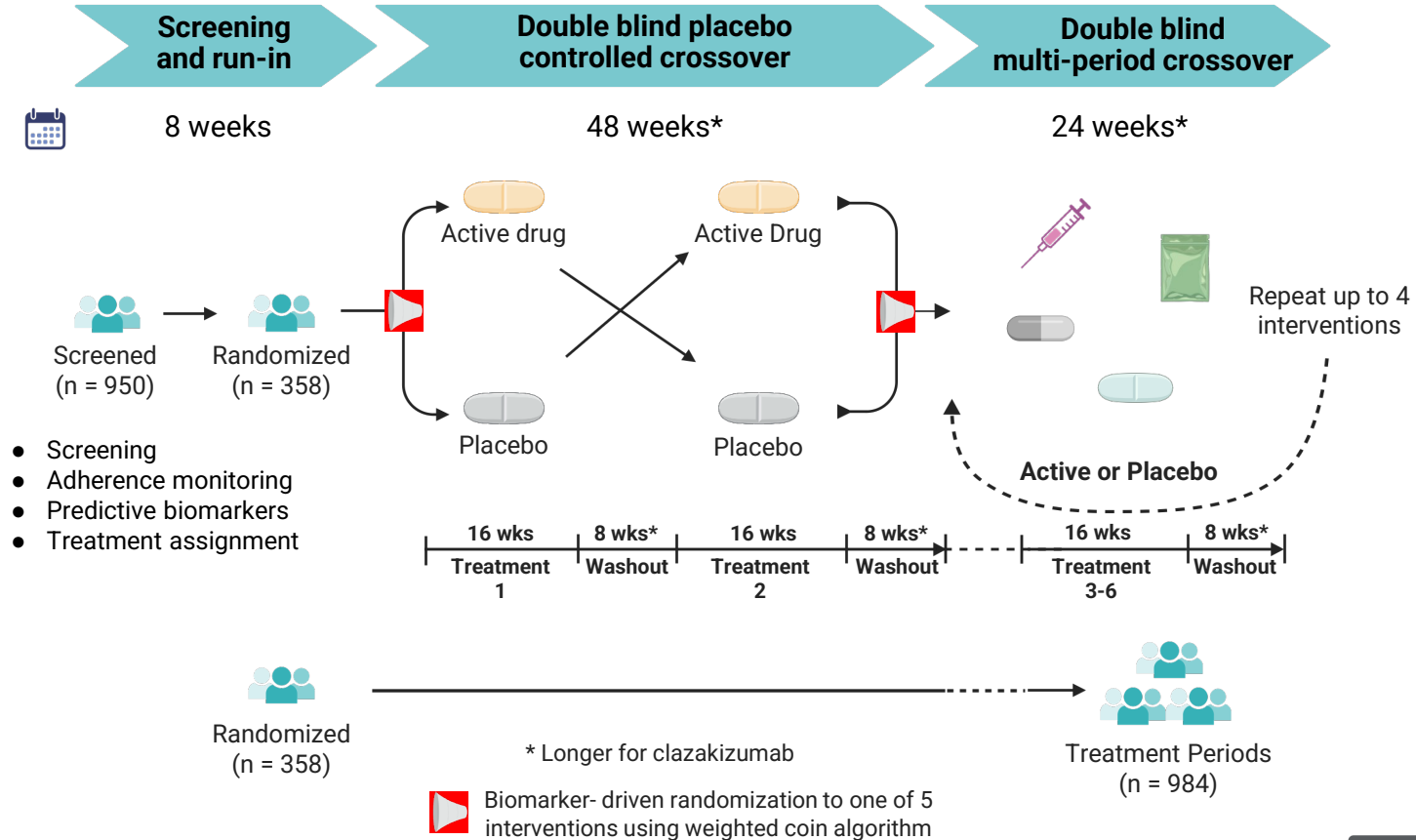


Medium Chain Triglycerides

Example for MCT

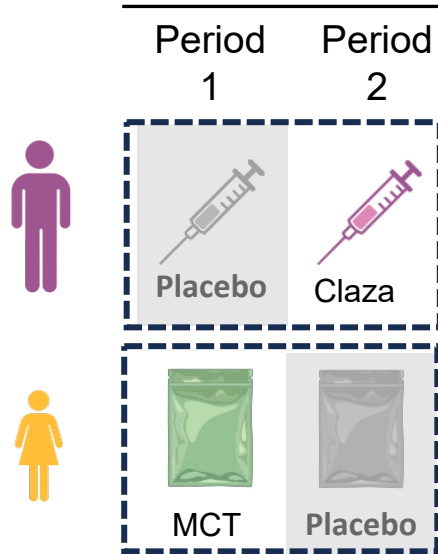


Multiperiod Crossover with Adaptive Enrichment

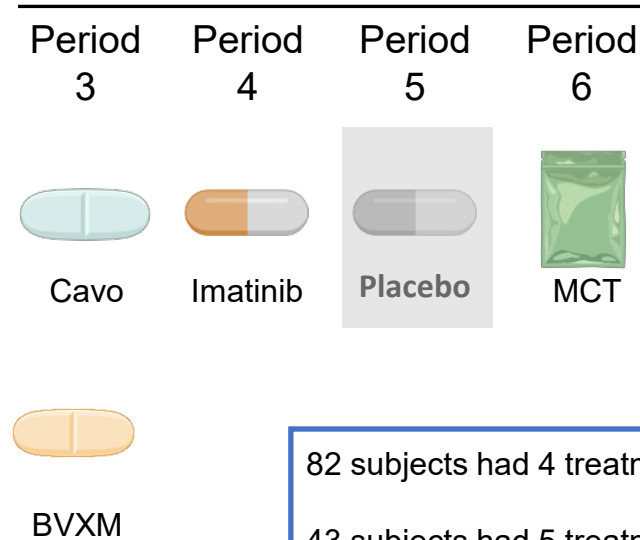


Examples of multi-period cross-over allocations in PrecISE

Two period crossover
with matched placebo



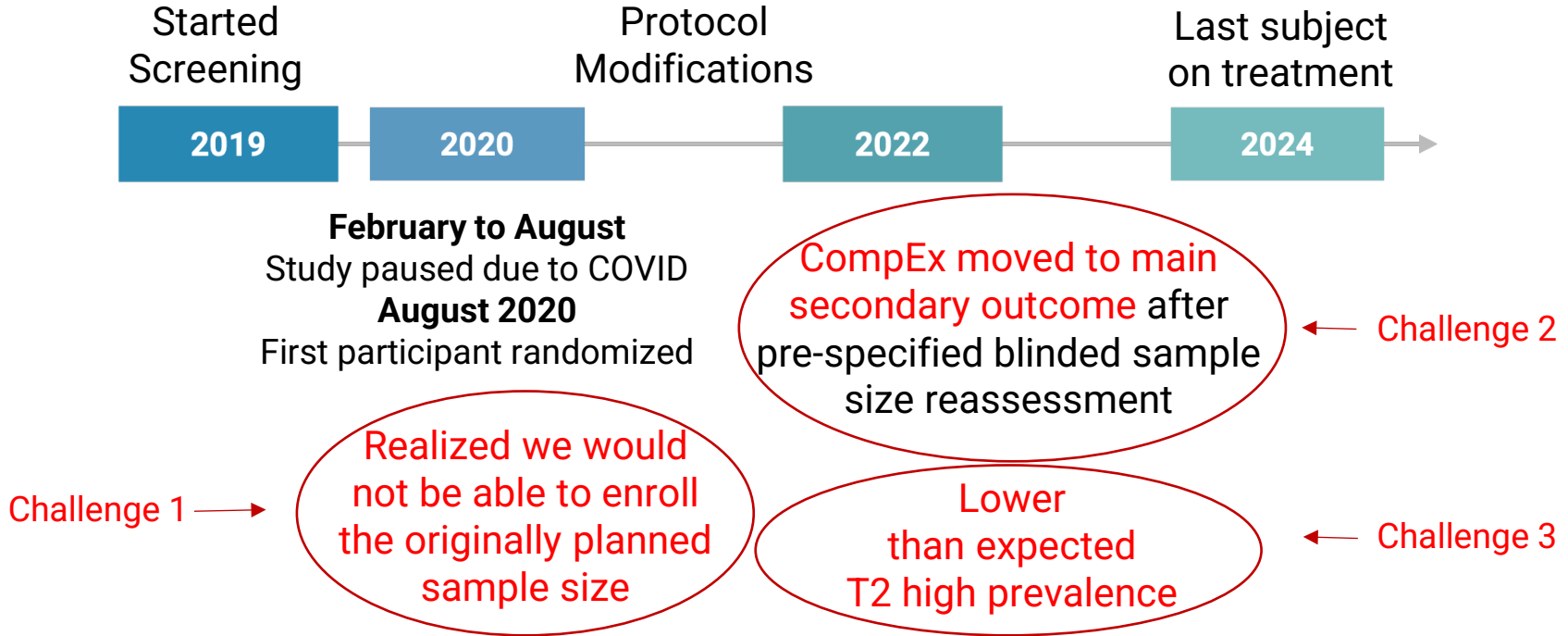
Multiperiod crossover with
up to one more placebo



Sensitivity analyses
accounting for placebo
mode and timing

82 subjects had 4 treatment periods (~2 years)
43 subjects had 5 treatment periods (~2.5 years)
12 subjects had 6 treatment periods (~3 years)

Milestones and Challenges



	Initial Design: 2018	Final Design: 2023	Reason
Primary endpoints	FEV1, ACQ, CompEx	FEV1, ACQ	Low within-subject correlation
Main Secondary	--	CompEx	
Subjects per arm	150	110	COVID
Number of interim analyses	2	1 or none	COVID
Biomarker positive to negative ratio, B+ to B-	67% of B+	≥50% of B+	Not enough T2 high
Number of subgroups in the final analysis	Test in all and B+	Test in all and 5 nested subgroups	No interim analysis, smaller sample size in B+

PrecISE: Baseline Characteristics total cohort

Adults n=329



Age = 52±13 yrs
66% female, 25% Black
≥2 exacerbations/yr = 29%
Biologic use = 28%
BMI = 33.0
Pre-BD FEV1 = 70%
ACQ=1.8

Blood Eos = 164
FeNO = 23
IL-6 = 3.5

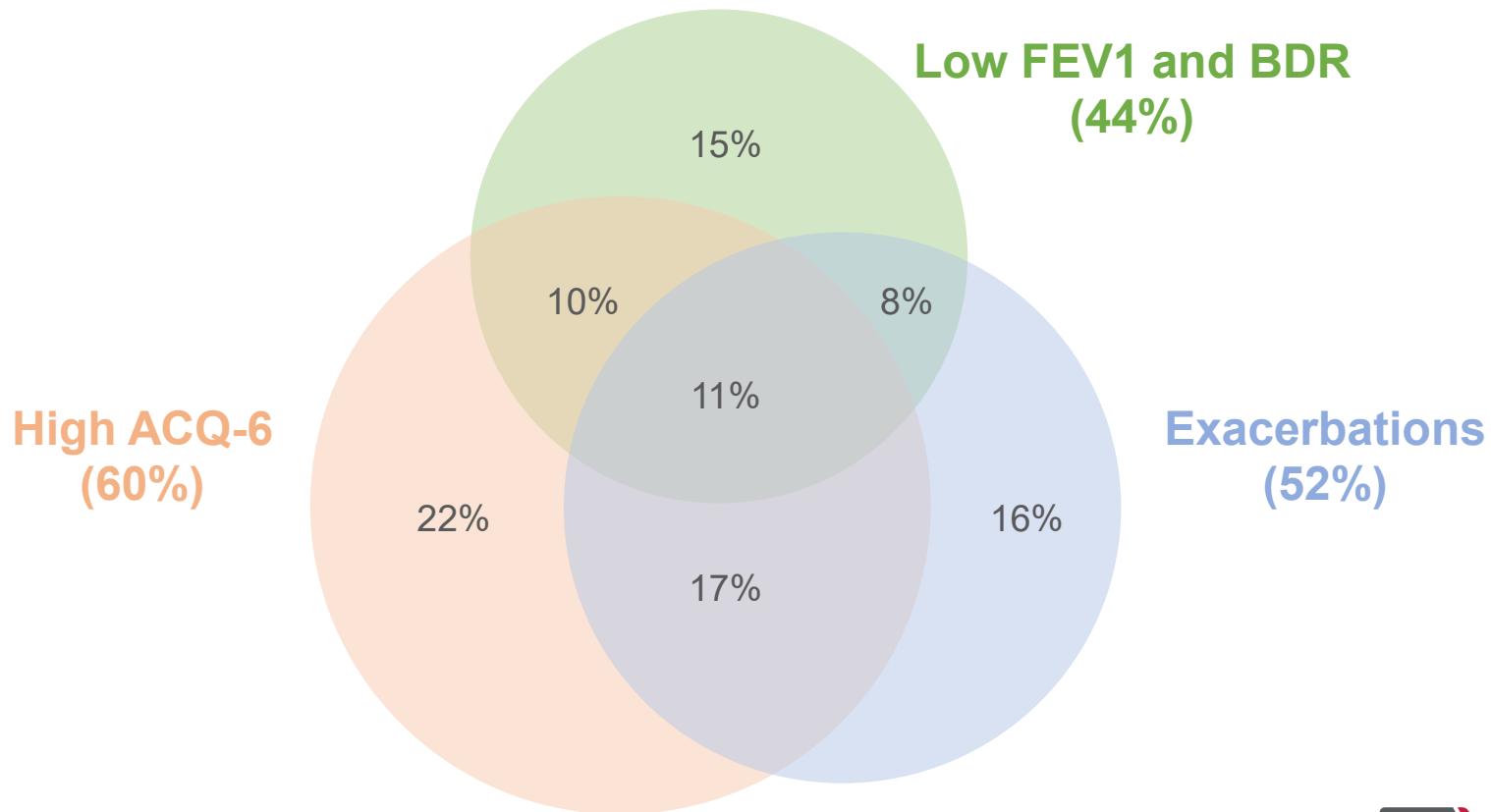
Adolescents n=29



Age = 15±2 yrs
55% female, 41% Black
≥2 exacerbations/yr = 35%
Biologic use = 21%
BMI = 29.3
Pre-BD FEV1 = 94%
ACQ = 1.2






Blood Eos = 159
FeNO = 37
IL-6 = 2.2

Uncontrolled Asthma Despite ICS/LABA Compliance at Compliance Visit



Baseline paper: Denlinger L et al, *J All Clin Immunol* 2026

Futility analyses of PrecISE interventions

	<u>Futility</u>	<u>Final Analysis</u>
 Medium Chain Triglycerides (n=135)	Continue all	All and biomarker positive
 Cavosonstat (n=113)	Stop biomarker negative (genotype)	Biomarker positive
 Imatinib (n=147)	Not done	All and nested subgroups
 Broncho-Vaxom (n=143)	Not done	All and nested subgroups
 Clazakizumab (n=138)	Not done	All and nested subgroups

Nested subgroups for three interventions

Imatinib



Biomarker Driven
Assignment



Eos < 400
Eos < 300
Eos < 225
Eos < 150
Eos < 100

**Broncho-
Vaxom**



Eos ≥ 350
Eos ≥ 300
Eos ≥ 250
Eos ≥ 200
Eos ≥ 150

Clazakizumab



IL-6 > 6
IL-6 > 4
IL-6 > 3.1
IL-6 > 2.5
IL-6 > 2

Final Efficacy Analysis

In entire population
and five nested
subgroups

Statistical power and analysis plan

- Investigate 5 interventions against placebo with 80% power to detect:
 - FEV1 6.5% change, ACQ 0.32 unit change, CompEx event rate ratio of 0.60
- **Modified Intention to Treat (mITT)** with at least one post baseline measurement
- **Mixed Model Repeated Measures (MMRM)** showing adjusted treatment effect (95% CI)
- Primary and secondary outcomes in biomarker positive groups
- Pre-specified exploratory groups including biomarker negative

PrecISE Results: Heat Map

	Medium Chain Triglycerides	Cavosonstat	Imatinib	Broncho-Vaxom	Clazakizumab
FEV1 % Pred					
ACQ-6					
CompEx Events		Genotype subgroup			



Potential benefit in biomarker positive subgroup*



Potential benefit in exploratory or biomarker negative subgroup*



Worse than placebo

PrecISE Results: Heat Map

	Medium Chain Triglycerides	Cavosonstat	Imatinib	Broncho-Vaxom	Clazakizumab
FEV1 % Pred			Blood Eos \geq 300		
ACQ-6	Adults FeNO < 15				IL-6 > 3.1
CompEx Events		Genotype subgroup			IL-6 > 3.1



Potential benefit in biomarker positive subgroup*



Potential benefit in exploratory or biomarker negative subgroup*



Worse than placebo

* Unadjusted p-value < 0.05

PrecISE Results: Heat Map

	Medium Chain Triglycerides	Cavosonstat	Imatinib	Broncho-Vaxom	Clazakizumab
FEV1 % Pred			Blood Eos \geq 300		
ACQ-6	Adults FeNO<15		Positive Treatment Effect (p>0.05)		IL-6 > 3.1
CompEx Events		Genotype subgroup	Positive Treatment Effect (p>0.05)		IL-6 > 3.1



Potential benefit in biomarker positive subgroup*



Potential benefit in exploratory or biomarker negative subgroup*



Worse than placebo

* Unadjusted p-value < 0.05

PrecISE conclusions: hypotheses generated

- Two biomarker / intervention pairs should not be pursued further:
 - Broncho-Vaxom for high eosinophils
 - Clazakizumab for high IL-6
- Three areas warrant further investigation

Mitochondrial metabolism
(Medium Chain Triglycerides,
low FeNO adults)

New markers of epithelial
/ arginine metabolism

Nitrosothiol metabolism
(Cavosonstat,
GSNOR SNP)

Study asthma
exacerbations

Mast cell c-kit
(Imatinib,
high Eos)

Newer generation
tyrosine kinase
inhibitors or c-Kit mAb

PrecISE - Accomplishments

- Evaluated five novel interventions in phase II proof-of-concept biomarker-driven precision medicine trial
 - Three first in asthma
- Master protocol with biomarker-driven adaptive enrichment
 - Novel trial design in severe asthma
- Efficient multiperiod cross-over design and feasibility of retaining subjects for up to three years
 - From 358 subjects to almost 1000 treatment periods
- Accomplished key RFA objectives despite reduced sample size
 - COVID adaptations including remote spirometry
- Fourteen publications to-date, 12 planned or in progress
- Serum, PBMS, sputum, and CT imaging biobank

Precision Medicine in Asthma: Future Directions

- Asthma biomarker profile is changing in the post-biologic era
- Adaptive platform trial designs are feasible in severe asthma
- Challenges identifying predictive biomarkers for T2 low asthma
- Need better point-of-care biomarkers of dysregulated immunity and airway structural defects to impact asthma natural history

PrecISE Acknowledgments

DMCC

Alison Marquis, Manager
Maria Sanchez

Protocol Design

Elliot Israel
Anastasia Ivanova

Ancillary Studies

Monica Kraft
Serpil Erzurum

Safety

Steve White
Dave Peden
Alison Burbank

Recruitment / Retention

Len Bacharier
Nick Kenyon

Spirometry Core

Loren Denlinger
Praveen Akuthota

Sputum Core

John Fahy

Imaging Core

Mario Castro

Biorepository

Suzy Comhair
Wanda O'Neal

Patient Advisory

Jerry Krishnan

DSMB

Rey Panettieri, Chair

NHLBI

Patricia Noel
Jim Kiley
Tom Croxton
Jining Liu

Industry Partners

CSL Behring: Clazakizumab
GlaxoSmithKline: Advair and Ventolin
Laurel Therapeutics: Cavosonstat
OM Pharma: Broncho-Vaxom®
Sun Pharma: Imatinib Mesylate
Vitaflo: Medium-Chain Triglycerides

Clinical Coordinators

Patient Volunteers