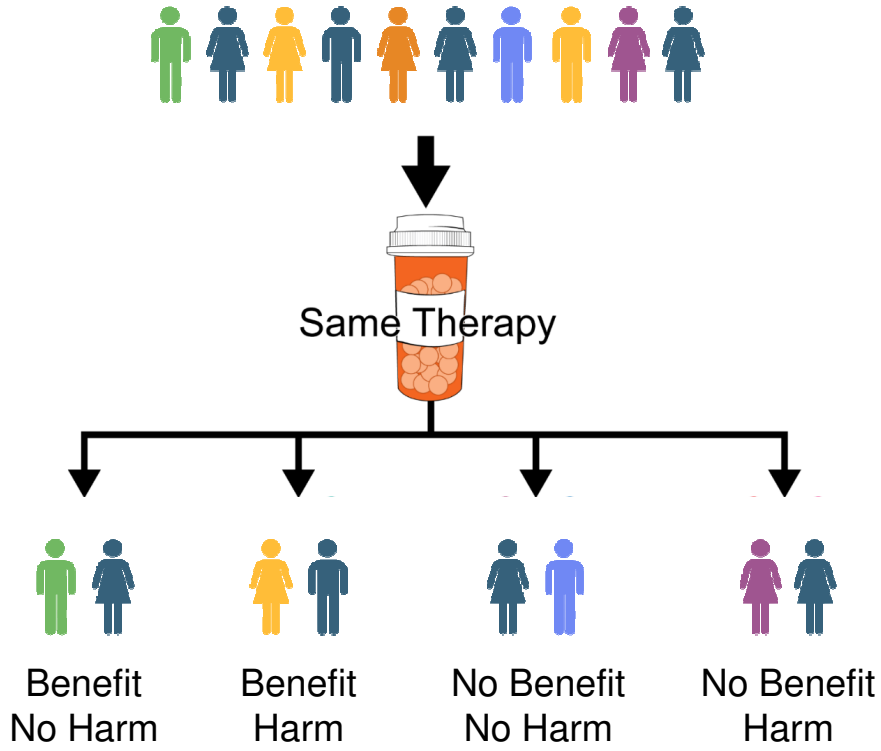
An overview of the PrecISE Trial

Steve N. Georas, M.D.
University of Rochester Medical Center
Rochester, NY
on behalf of PrecISE investigators

Without Precision Medicine

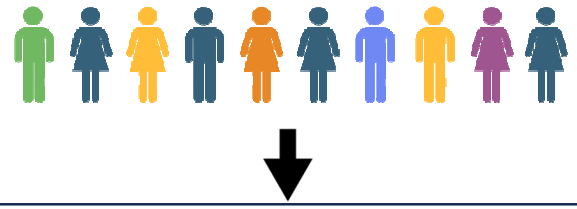


(Adapted from J. Gregory ©2019)

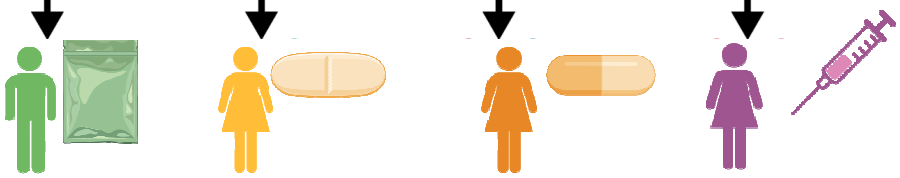
The Promise of Precision Medicine

Biomarker-driven Therapy

Predictive Biomarker



Monitoring Biomarker



PreclSE
PRECISION INTERVENTIONS FOR SEVERE ASTHMA

(Adapted from J. Gregory ©2019)

NIH National Heart, Lung, and Blood Institute

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

Patricia Noel

Jim Kiley

Request for Applications issued 2017 by NHLBI

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

Innovative trial design
Use predictive and monitoring biomarkers

Platform Trial with Master Protocol
Biomarker-driven Adaptive Enrichment

Innovative interventions

Five interventions
3 first in asthma

PrecISE
PRECISION INTERVENTIONS FOR SEVERE ASTHMA

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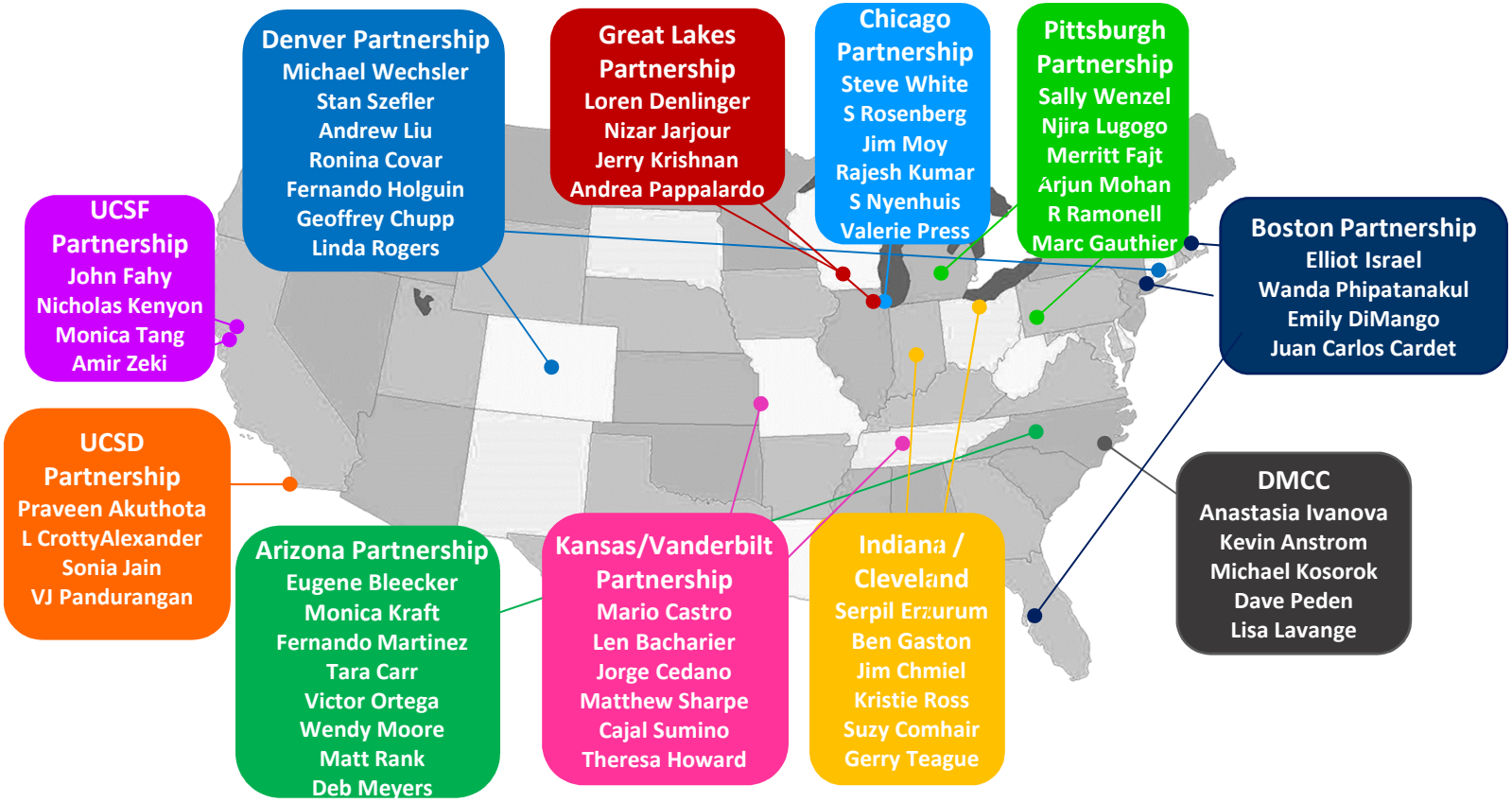
PrecISE Network



PrecISE
PRECISION INTERVENTIONS FOR SEVERE ASTHMA

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

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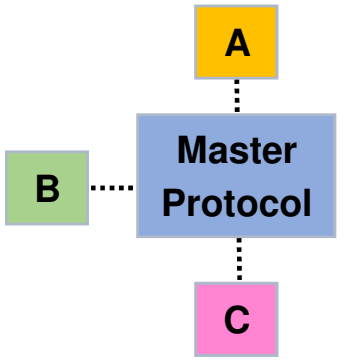
PrecISE Protocol: Initial Design

- 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**:



FEV_1
(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
Ivanova et al, *J Biopharm Stat*, 2020
Israel et al, *J All Clin Immunol*, 2021

Inclusion and Exclusion Criteria

Inclusion

- Male or female, age ≥ 12 years
- Verification of asthma by MBR > 12% or hyperresponsiveness to methacholine
- On stable therapy x2 months, at least medium dose ICS + 2nd controller
- Meet ERS/ATS guideline criteria for severe asthma

Exclusion

- Investigational drug administration within the past 60 days OR < 5 half-lives
- Diagnosis of other chronic pulmonary disorders
- Daily systemic corticosteroids above 10 mg prednisone / day
- Smoking history (age related cut-offs; 5 to 15 pack-years)
- Additional safety criteria to mitigate risk while supporting recruitment

Uniform single consent

First in asthma

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

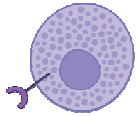
First in asthma

Medium Chain Triglycerides
Mitochondrial metabolism
Biomarker: FeNO ≥ 15 ppb
Partner: Vitaflo/Nestle
WG Chair: S. Erzurum

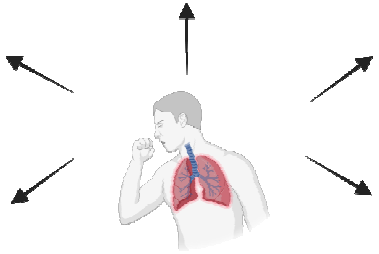
Imatinib
Mast cell c-Kit tyrosine kinase
Biomarker: Eos < 300/µl
Partner: Sun Pharma
WG Chair: E. Israel

S-Nitrosothiols

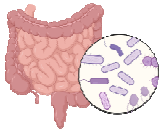
Mitochondrial Metabolism



Mast Cell c-Kit



Immune Modulation



Systemic Inflammation

Broncho-Vaxom
Immune modulation
Biomarker: Eos ≥ 300/µl
Partner: OM Pharma
WG Chair: F. Martinez

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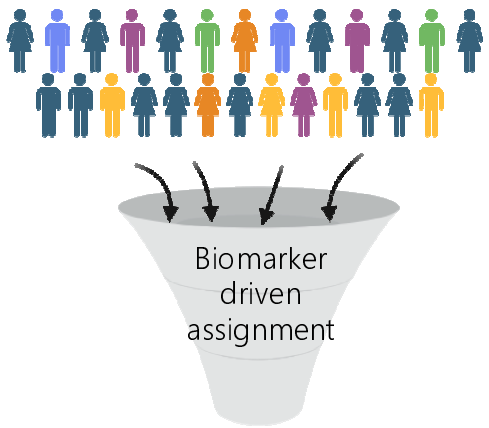
Clazakizumab
Anti-IL-6
Biomarker: IL-6 > 3.1 pg/ml
Partner: CSL Behring
WG Chair: J. Fahy

First In asthma

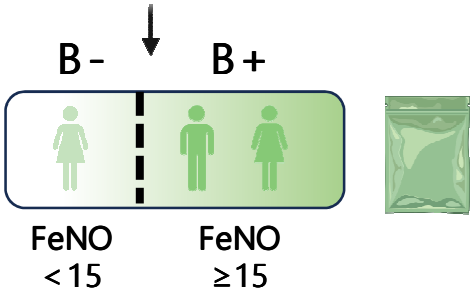
Because of uncertainty about cut-off values, Biomarker Positive (B+) and Biomarker Negative (B-) included in all interventions

Oversample B+, and adjust after interim analyses



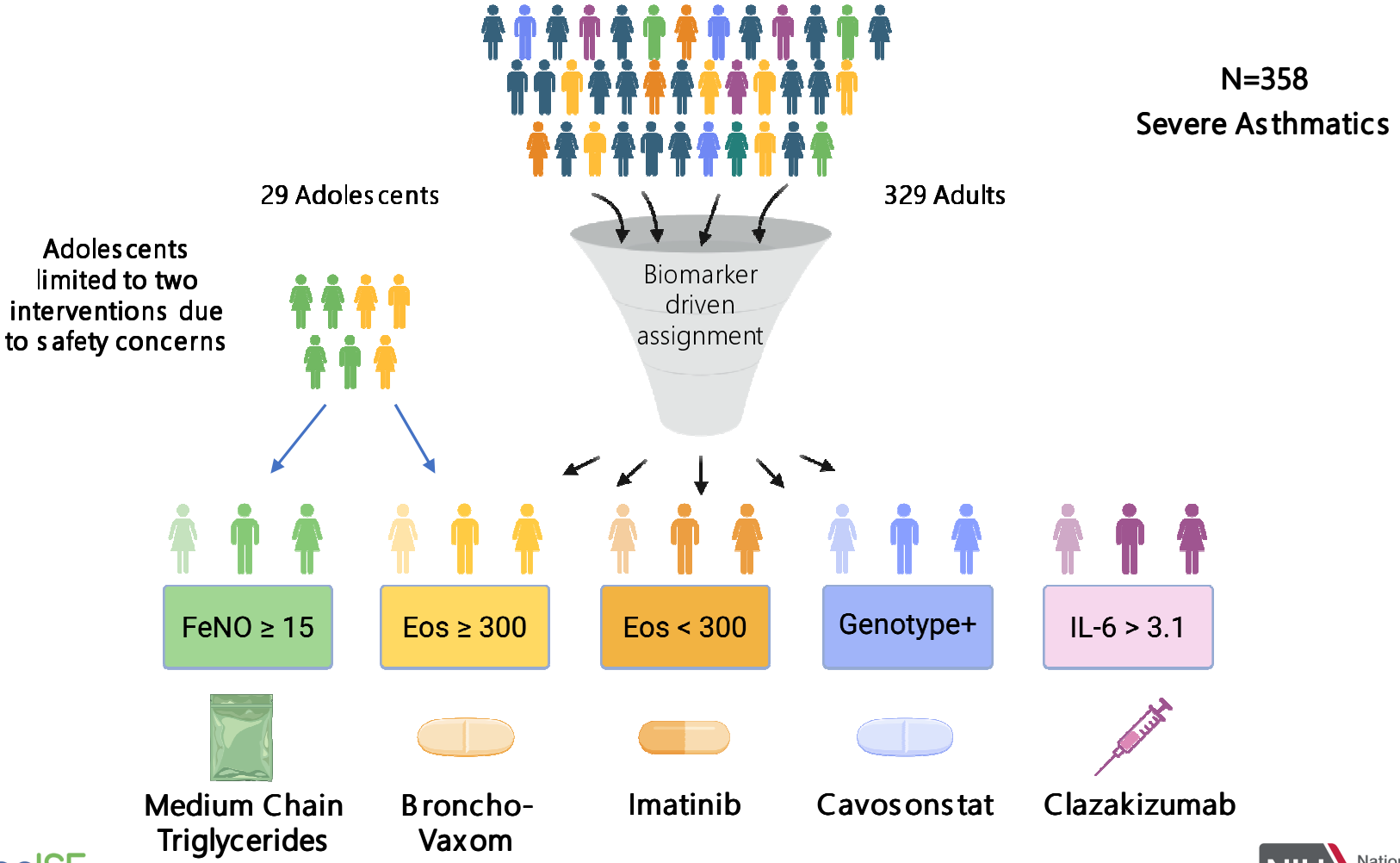
FeNO

Medium Chain Triglycerides



Example for MCT

Ivanova et al, *J Biopharm Stat*, 2020; Li et al, *Biometrics*, 2024



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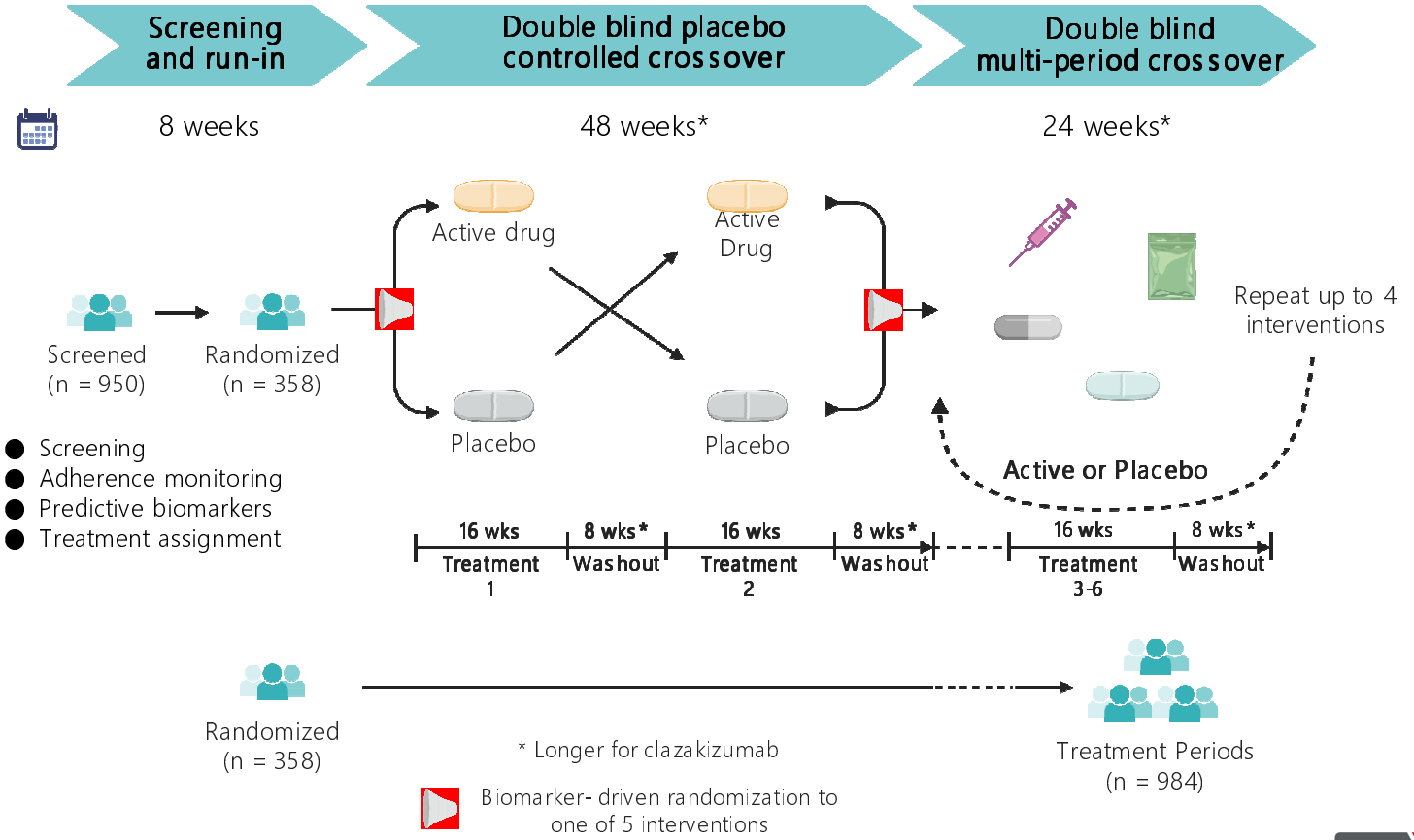
Multiperiod Crossover with Adaptive Enrichment



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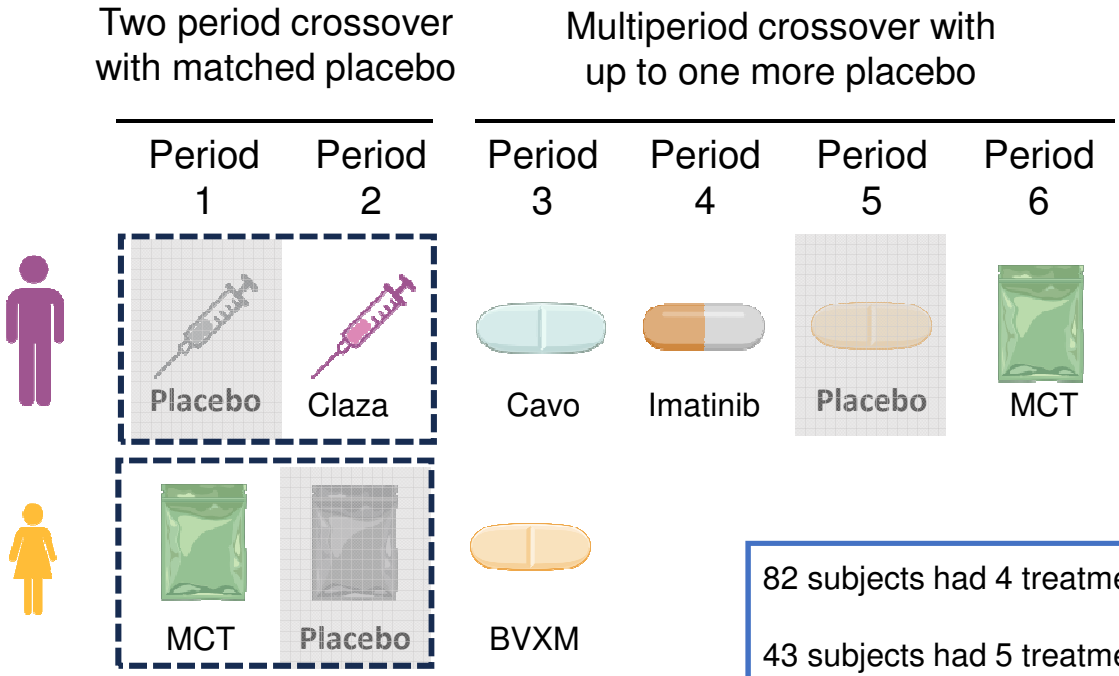
Examples of multi-period cross-over allocations in PrecISE



Sensitivity analyses accounting for placebo mode and timing

82 subjects had 4 treatment periods (~2 years)

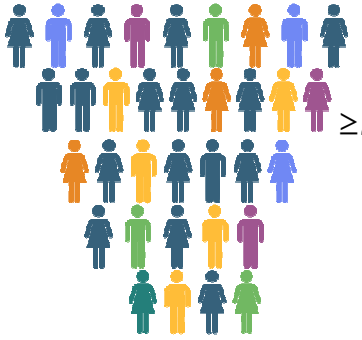
43 subjects had 5 treatment periods (~2.5 years)

12 subjects had 6 treatment periods (~3 years)

Ivanova et al, *J Biopharm Stat*, 2020; Song et al, *Stat Biopharm Res*, 2024

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

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PrecISE Accomplishments

- Evaluated five novel interventions in phase II proof-of-concept biomarker-driven precision medicine trial
  - Three first in asthma
- Developed a master protocol 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
- Eleven (11) publications to-date