PrecISE: Precision Interventions for Severe and/or Exacerbation-Prone Asthma Network

National Clinical Trial (NCT) Identified Number: NCT04129931

IND Sponsor: University of North Carolina at Chapel Hill

Funded by: National Heart, Lung, and Blood Institute

Version Number: v 3.3

27 September 2024

STATEMENT OF COMPLIANCE

The PrecISE study will be conducted in accordance with International Council on Harmonization E6 Guideline for Good Clinical Practice (ICH E6 GCP), applicable United States (US) Code of Federal Regulations (CFR), and the NHLBI Terms and Conditions of Award. The study is being conducted under an Investigational New Drug application (IND) from the US Food and Drug Administration (FDA), and Dr. David B. Peden, MD, MS of the University of North Carolina at Chapel Hill is the IND sponsor. The PrecISE Principal Investigators will assure that no deviation from or changes to the protocol will take place without prior agreement from Dr. Peden (as IND sponsor) and the NHLBI (as funding agency), FDA review, and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the central IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. When changes are made to the consent form; a determination will be made regarding whether a new consent needs to be obtained from participants who had provided consent earlier using a previously approved consent form.

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	The PrecISE (Precision Interventions for Severe and/or Exacerbation-Prone Asthma Network) Study
Background and Rationale	PrecISE is an NHLBI-sponsored network established to conduct a phase 2 proof-of-concept study to test interventions in biomarker-defined subgroups of patients with severe asthma. Severe asthma affects 5 - 10% of all patients with asthma (~2.5 million Americans), and patients with severe asthma experience substantial morbidity and require extensive use of healthcare resources.[1] Despite the use of high dose inhaled corticosteroids and a second controller (and/or systemic corticosteroids), severe asthma patients continue to have poor control, low lung function and/or increased risk of severe exacerbations. Consequently, there is a need to investigate novel interventions for utility as targeted therapies in this patient population. The PrecISE Investigators proposed novel interventions in biomarker-based subgroups, with the goals of gaining information about the efficacy of the interventions in the severe asthma patient population and additional information on the utility of the biomarkers in identifying patients for treatment. Over 30 interventions were proposed, and six were selected by the PrecISE Steering Committee for initial study based on feasibility, scientific enthusiasm about preliminary evidence of efficacy, safety, and potentially useful biomarkers. Additional interventions were identified for consideration as the study progresses, particularly if any of the initial interventions are discontinued during the study for low

likelihood of success or safety issues. Due to delays incurred by the Covid-19 pandemic, the number of interventions to be initially investigated was reduced to five.

All interventions will be studied under one master protocol using an adaptive platform trial design[2,3] to assess multiple interventions simultaneously, while also obtaining information on biomarker utility in predicting responsiveness to each treatment. Interventions may be discontinued and new interventions entered into the study, as data accrue on the safety and efficacy of the various interventions. Definitions of patient subgroups targeted by each intervention and the biomarkers used to define them are adapted prospectively during the study. By prospectively enriching patient population we increase the chance of demonstrating a treatment effect at the end of the trial, as testing the efficacy of an intervention in an unenriched population of all participants may results in failure to detect the treatment effect.

The master protocol, described in the following sections (1.2 – 10.4), contains all aspects of the study design and all study elements and procedures common across the various interventions. Details of each of the interventions planned for study, including the rationale for their selection into the study and intervention-specific study procedures required for each, are provided in Appendices I-V. As additional interventions are selected for study, appendices for each will be added to the master protocol as protocol amendments and submitted to the DSMB and IRB for their approval and to the FDA for its review prior to implementation.

Our approach to designing PrecISE provides flexibility in studying multiple novel interventions at the same time and adaptability in defining patient subgroups targeted for therapy and in stopping some interventions and starting others through interim decision-making utilizing accruing data. The anticipated result is a wealth of information about the efficacy and safety of new treatments for severe asthma and about which patients might benefit from those treatments in the future, providing a precision medicine solution in an area of significant unmet medical need.

Overall Study Description:

The PrecISE Study is an adaptive platform trial conducted under a single Master Protocol to identify new therapies for severe asthma that are effective in biomarker-defined subgroups of participants. Five novel therapies will initially be investigated. The trial is designed to meet our primary objectives, namely, to: (1) identify novel therapies that work in biomarker-defined subgroups of participants with severe asthma, and (2) optimize the subgroups targeted for treatment by refining the biomarker and subgroup definitions.

For each participant, the study consists of three phases: (i) an initial screening phase, (ii) a 2-period crossover phase, and (iii) a single-period

crossover phase with successive re-randomizations. Common platforms for biomarker screening will be used during the initial screening period to determine a participant's biomarker profile. Throughout the study, interventions will be randomly assigned based on these biomarker profiles. Participants will have a higher likelihood of assignment to an intervention that targets their particular profile. Subgroup definitions and associated treatment assignment probabilities are adapted as data accumulate throughout the study.

Following the initial screening period, participants will be randomly assigned to interventions based on their biomarker profile and enter a 2-period, double-blind crossover phase consisting of two 16-week treatment periods separated by an 8-week washout period. Note that longer washout periods will be considered for therapies with a half-life longer than 11 days. Treatment sequence will be randomly assigned as either test treatment followed by matching placebo or vice-versa.

At the conclusion of the 2-period crossover phase and washout period, participants enter the single-period crossover phase of the study consisting of successive single 16-week treatment periods followed by 8-week (or longer) washout periods. For each single-period crossover treatment, participants are randomly assigned to interventions based on their biomarker profiles that were determined during the initial screening period. The biomarker-based treatment assignment probabilities will be adapted during the study as data on the utility of the biomarkers in predicting treatment response accumulate.

A small percentage of participants will receive placebo in this phase (periods 3-6) to assess seasonal and sequence effects throughout the study (no participant will receive more than three placebos during the study). Masking of treatment assignments will be maintained by matching a participant's placebo to one of the available interventions for which the participant is eligible and has not yet received.

Periodic reviews of safety data will be performed by the Data and Safety Monitoring Board (DSMB) at pre-specified intervals throughout the study, and interventions found to pose significant safety risks in the severe asthma population will be dropped from the study.

Interventions may enter the study at different times, depending on their availability, and may be discontinued, as noted above. Additional interventions may be proposed depending on the progress of the study and innovations in potential treatments for severe asthma.

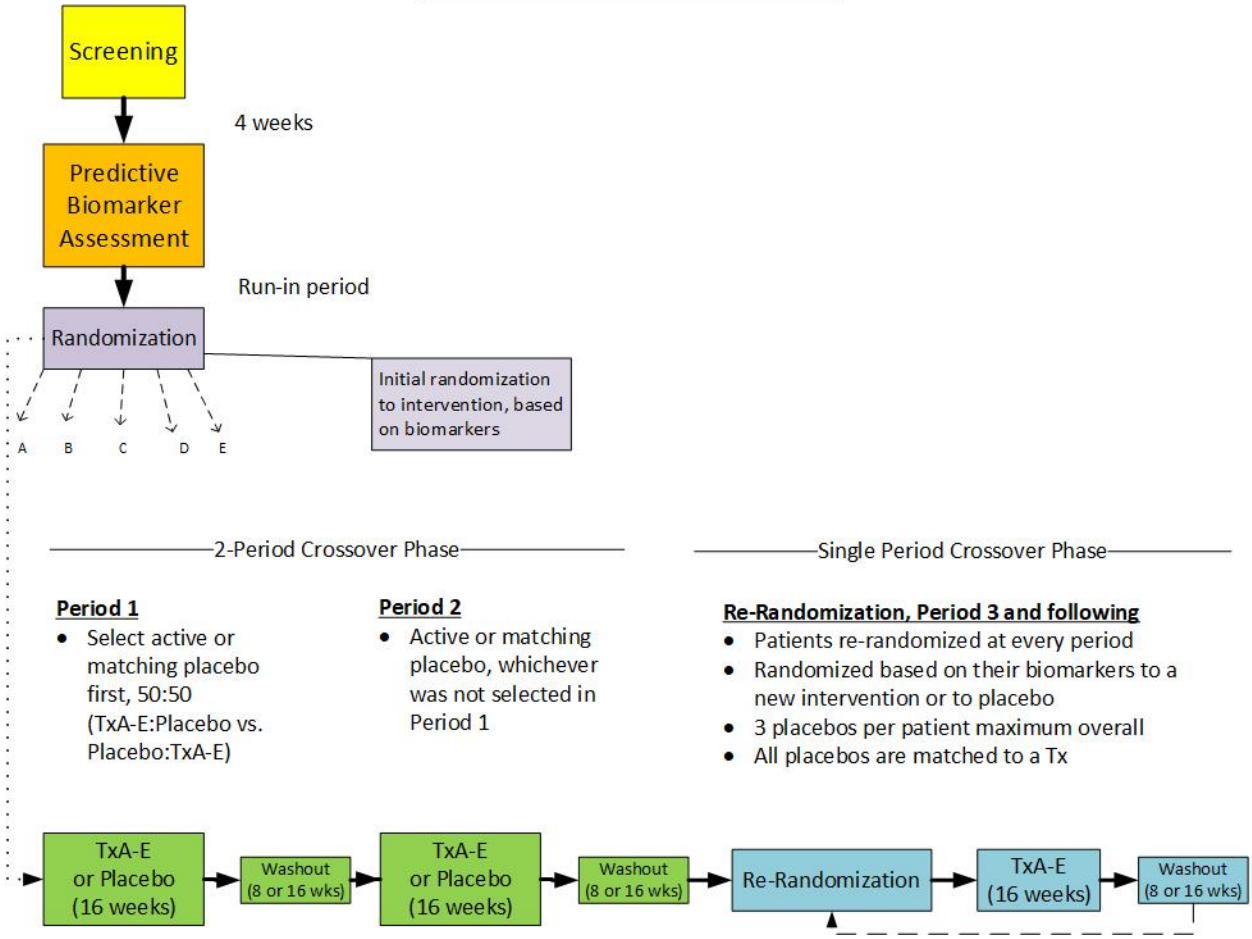
Our study timelines and enrollment goals are such that, depending on the time of enrollment, each participant will receive up to five test treatments

Objectives:	**Primary Objectives:** (1) Identify novel therapies that work in biomarker-defined subgroups of severe asthmatic participants; (2) Optimize the subgroups targeted for treatment by refining the biomarkers and subgroup definitions. **Secondary Objectives:** (1) Gain information about potential response/pharmacodynamic biomarkers for selected therapies; (2) Explore the safety and effectiveness of selected therapies in adolescent participants with severe asthma.
Endpoints:	**There are 2 primary efficacy endpoints:** **1) FEV_1 percent predicted,** assessed prior to bronchodilator administration **2) Asthma symptom control,** assessed via the Juniper Asthma Control Questionnaire (ACQ-6)
Study Population:	The sample will include 395 adult and pediatric (12-18 years of age) participants who meet modified guideline criteria for severe asthma and who are currently uncontrolled or continue to have exacerbations. Participants must be at least 12 years of age, on a stable regimen of asthma medications prior to enrollment, and satisfy other inclusion/exclusion criteria. Not all interventions will be studied in adolescents (see Appendices I-V). We anticipate that at least two of the interventions will be studied in both adults and adolescents.
Sample Size:	A sample size of 111 participants is required to achieve 80% power to detect a treatment effect with respect to at least one of the two primary endpoints (FEV_1 or asthma symptom control) equal to 0.3 times the standard deviation of that endpoint, taking into account the possibility to stop for futility and assuming a treatment period discontinuation rate (active or placebo) of 10%. The Type I error probability will be controlled under the global null hypothesis (no effect on either endpoint) at $\alpha \leq 0.10$ (see Section 9.2). A sample size of 111 participants, at least 74 targeted by the intervention, is required to support the final precision medicine analysis. Secondary efficacy analyses will be conducted in pediatric participants, but power to support hypothesis testing will be limited for these analyses.
Interim Analysis:	Interim analyses will be conducted for the following purposes. (1) A single interim analysis for futility may be conducted for each test treatment based on data from the a priori best subgroup, biomarker positive, patents. Test treatments demonstrating futility will be dropped from the trial. A futility analysis will be also performed in biomarker negative patents. Further enrollment to test treatments demonstrating futility in biomarker negative subgroup will be limited to biomarker positive participants. (2) An interim analysis to estimate the within-participant, between-period correlation might be conducted pooling data across test and placebo treatment periods, maintaining the masking of treatment assignments. If the correlation is much higher than we hypothesized, we

Final Analysis:	will reduce the required sample size prior to unmasking of treatment assignments and modify the final analysis plan to reflect this change. The timing of these interim analyses, will depend on the time the treatment is available to enter the Master Protocol, as well as participant accrual. An intervention will be considered effective if it is effective on at least one of the two primary outcomes. The analysis model for the final efficacy analysis will take into account the correlations on outcomes assessed for the same patient across the different treatment periods. The final analysis will include pairs of the treatment and matching placebo from the first two periods of the trial, as well as unmatched observations on the same patient. Mixed model repeated measures methods will be used for the primary analysis (see Section 9.5).
Phase:	Phase 2 proof-of-concept study
Description of Sites/Facilities Enrolling Participants:	Approximately 35 U.S. sites; all sites are clinic settings.
Description of Study Intervention:	Five novel treatments for severe asthma will be studied, each targeting a specific, biomarker-defined subgroup of participants. Candidates currently include novel medications and dietary supplements that target mechanisms relevant to asthma pathology.
Study Duration:	Approximately 62 months from first participant screened until last participant follow-up
Participant Duration:	**Treatment Supply:** Participant duration will be variable based on the time they enter the study and the number of treatments for which they are eligible (see Section 4.4). We anticipate needing approximately 850 months of treatment (active or placebo) for each intervention.

1.2 SCHEMA

PrecISE Protocol Schema



1.3 SCHEDULE OF ACTIVITIES (SOA)

PrecISE Visit Structure **Procedures**	**Visit SA: Screening**	**Visit SB: Optional as needed to qualify**	**Visit SC: Compliance check***	**Visit 0: Run-In Visit, Safety Labs & Biomarkers**	**Visit X.1: Treatment Visit 1**	**Visit X.2: Treatment Visit 2**	**Visit X.3: Treatment Visit 3**	**Visit X.4: Treatment Visit 4**	**Visit X.5: End of Treatment Visit**	**Visit X.6: Washout**
Consent, Demographics, Contact Info, Registry[1]	X									
Complete Physical Exam	X	X			X					
Brief Physical Exam by Coordinator				X		X[4]	X	X[4]	X	X[11]
CompEx Diary Assessment[1]			X	X	X	X	X	X	X	X[11]
Compliance Assessment[1]			X	X	X	X	X	X	X	X[11]
Dispense Controller Medication[1]	X	X		X	X	X	X	X	X	X[11]
Dispense and train on e-diary and home spirometers[1]	X	X		X						
Assess that participant meets or continues to meet inclusion criteria[1]				X	X					X[11]
Intervention Assignment (occurs between visits 0 and 1.1 for the first period) [1]				X						X[11]
Treatment Assignment (active or placebo) [1]					X					
Dispense Study Treatment[1]					X	X	X	X		
Medical, Asthma and Allergy History questionnaires[1]	X	X								X
Adolescent School questionnaire (participants in school only) [1]	X									
Validated questionnaires (to determine sleep apnea, GERD, depression, sinus disease, vocal cord dysfunction) [1]	X	X								

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Validated questionnaires for Quality of Life and Work Productivity[1]	X	X			X	X	X	X	X	
Socioeconomic information/Household[1]	X									
Asthma and non-asthma medication (concomitant medications) status[1]	X	X		X	X	X	X	X	X	X
Blinding Index questionnaire									X	
Pulmonary Function, Asthma Control and Exacerbations										
Spiro PRE with specified med withholds[2]	X	X		X	X	X	X	X	X	X[11]
Spiro POST 4 puffs albuterol[2]				X	X				X	
Maximum Bronchodilator (4 + 2 + 2 puffs albuterol)	X			X[3]						
Methacholine challenge (if needed)		X								
DLCO (if needed bc +smoking Hx)		X								
Cotinine (if needed bc +smoking Hx)		X								
ACQ-6[1]	X			X	X	X	X	X	X	X
Exacerbation History/Health care utilization questionnaire[1]	X			X	X	X	X	X	X	X
Safety Assessments										
Urine: Pregnancy test (females of childbearing potential)	X	X		X	X	X[4]	X	X[4]	X	X[11]
Blood: CBC with Differential Count				X	X	X[4]	X	X[4]	X	X[11]
Blood: Chemistry Panel (including liver function tests)				X	X	X[4]	X	X[4]	X	X[11]
Blood: Triglycerides (non-fasting)				X						

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Blood: Viral screens – Hep B and C, HIV Types 1 and 2				X						
Blood: TB via QuantiFERON[5]				X						
Radiology (CXR), not required if the participant has a negative QuantiFERON[5]				X						
Cardiology (EKG)				X						
Adverse event assessment[1]	X	X	X	X	X	X	X	X	X	X
Primary Predictive Biomarkers										
Blood eosinophils (CBC with diff)				X	X					
Plasma IL-6				X						
FeNO				X	X					
Genotyping				X						
Response/pharmacodynamic biomarkers										
Blood eosinophils (CBC with diff)						X[4]	X	X[4]	X	X[11]
Plasma IL-6										
FeNO						X[4]	X		X	
Additional Phenotyping Procedures										
Sputum induction[6]				X						
CT scan for lung phenotyping[6]				X						
Blood: PBMCs[7]					X[8]				X	
Urine for biorepository					X		X		X	
Blood for RNA[9]				X						
Other blood (plasma, serum) for biorepository					X	X[4]	X	X[4]	X	
Nasal EPX[10]				X	X		X		X	

*Visit SC is optional. All other visits are approximately 4 weeks apart. Treatment visits X.1-X.6 are repeated each treatment period.

[1] These procedures and assessments may be conducted remotely via phone, videoconference or electronic survey methods.

[2] Spirometry may be conducted in the home and/or in the clinic.

[3] Optional at site discretion to demonstrate reversibility

[4] Not required for adolescents at VX.2 and VX.4.

[5]Blood for TB via QuantiFERON is collected on adults only

[6] If not collected before V1.1, the Sputum and CT can be collected before or at V2.1 or before or at V3.1. Sputum induction and CT scans may not be conducted at all sites.

[7] PBMCs may not be collected at all sites.

[8] PBMC is only collected at V1.1.

[9] Blood for RNA if not collected before V1.1, should be collected at V2.1, and, again, at V3.1.

[10] Nasal EPX can be skipped if the institution requires a COVID test before the procedure. Nasal EPX collection is optional at the site level.

[11] Not required at the final VX.6.

Note: Due to the COVID-19 pandemic, not all procedures will be conducted at all clinic visits.