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organization, procedures, and interventions

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Abstract

Asthma is a heterogeneous disease, with multiple underlying inflammatory pathways and structural airway abnormalities that impact disease persistence and severity. Recent progress has been made in developing targeted asthma therapeutics, especially for subjects with eosinophilic asthma. However, there is an unmet need for new approaches to treat patients with severe and exacerbation-prone asthma, who contribute disproportionately to disease burden. Extensive deep phenotyping has revealed the heterogeneous nature of severe asthma and identified distinct disease subtypes. A current challenge in the field is to translate new and emerging knowledge about different pathobiologic mechanisms in asthma into patient-specific therapies, with the ultimate goal of modifying the natural history of disease. Here, we describe the Precision Interventions for Severe and/or Exacerbation-Prone Asthma (PrecISE) Network, a groundbreaking collaborative effort of asthma researchers and biostatisticians from around the United States. The PrecISE Network was designed to conduct phase II/proof-of-concept clinical trials of precision interventions in the population with severe asthma, and is supported by the National Heart, Lung, and Blood Institute of the National Institutes of Health. Using an innovative adaptive platform trial design, the PrecISE Network will evaluate up to 6 interventions simultaneously in biomarker-defined subgroups of subjects. We review the development and organizational structure of the PrecISE Network, and choice of interventions being studied. We hope that the PrecISE Network will enhance our understanding of asthma subtypes and accelerate the development of therapeutics for severe asthma.

Keywords

Severe asthma; precision medicine; adaptive clinical trial design; asthma exacerbation; type 2 asthma; non–type 2 asthma; patient advisory committee; biomarker

1. INTRODUCTION

Asthma is a highly heterogeneous disease, with multiple underlying inflammatory pathways and structural airway abnormalities that impact disease persistence and severity.[1,2] Although recent progress has been made in developing targeted asthma therapeutics, there is an unmet need for new approaches to treat patients with severe and exacerbation-prone asthma, who contribute disproportionately to disease burden.[3,4] For example, while approximately 3% to 10% of adult patients with asthma have severe disease, care of these patients accounts for more than 60% of asthma-related health care expenditures. Extensive deep phenotyping has revealed the heterogeneous nature of severe asthma and identified distinct disease subtypes.[5,6] A current challenge in the field is to translate new and emerging knowledge about distinct pathobiologic mechanisms in asthma into patient-specific therapies, with the ultimate goal of modifying the natural history of disease. This approach would be superior to achieving symptom control only, while the underlying intrinsic disease process continues.

To address these unmet needs, the National Heart, Lung, and Blood Institute (NHLBI) developed the concept for a precision intervention, adaptive clinical trials network, which was outlined in a request for applications (RFA) in 2016 (RFA-HL-17-009). The RFA encouraged innovation in trial design and data analysis, in the selection of interventions to be evaluated, and in the identification of patient phenotypes that each intervention should target. The RFA pointed out that our rapidly expanding understanding of diverse pathobiologic mechanisms in asthma provides an opportunity to leverage this knowledge base and develop more precise, biologically based approaches for asthma management and potentially disease modification. The Precision Interventions for Severe and/or Exacerbation-Prone Asthma (PrecISE) Network was formed in response to the RFA, and is a groundbreaking collaborative effort of leading asthma researchers and biostatisticians from around the United States. The PrecISE Network was designed to conduct adaptive, phase 2/proof-of-concept clinical trials of precision interventions in the population with severe asthma. Evaluation of potential predictive and monitoring biomarkers to guide the use of each intervention was also required.

Study objectives, and overview of trial design and statistical analysis plans

The primary objectives of the PrecISE Network are to (1) identify novel therapies that are efficacious in predefined biomarker-based subgroups of patients with severe asthma and (2) optimize the subgroups targeted for treatment by refining the biomarkers and subgroup definitions. Secondary objectives include (1) to gain information about potential monitoring biomarkers for selected therapies and (2) to explore the safety and effectiveness of selected therapies in adolescent patients with severe asthma. To meet these objectives, we developed a master protocol using an adaptive platform design to provide proof of concept for up to 6 precision intervention therapies (see Table I). Our trial design allows for the evaluation of multiple treatments in patients with different types of asthma within the same overall trial structure. The benefits of a master protocol to evaluate multiple therapies include the development of infrastructure to streamline trial logistics, improve data quality, and facilitate data collection and sharing across therapies.[7] Furthermore, the use of a common protocol that incorporates innovative statistical approaches to study design and data analysis allows for a broader set of objectives to be met more effectively than would be possible in independent trials of each therapy.[7] The use of an adaptive platform trial conducted under a master protocol allows flexibility in that interventions can enter the study when they become available, and leave the study at different times and for different reasons, including stopping early for futility or graduating for further study to support regulatory approval.[8]

We reported the PrecISE study design in a recent publication in the *Journal of Allergy and Clinical Immunology*.[9] Key features include the use of a cross-over design that allows patients to receive multiple interventions during the 32-month study. Treatment allocation is designed such that subjects expected to benefit from a particular intervention based on their biomarker profiles are more likely to receive that intervention, and the adaptive design allows for the target subgroup of each intervention to be refined on the basis of accumulating data during the study. After a screening and run-in period, subjects proceed to an initial double-blind placebo-controlled cross-over phase, followed by multiple cross-over phases for the remainder of the trial (Fig 1, reproduced from

Israel et al[9]). There are 3 primary efficacy outcomes: (1) airway function (FEV_1), (2) symptoms (6-item Asthma Control Questionnaire [ACQ-6]), and (3) asthma exacerbations and loss-of-control events as a substitute for exacerbations, using the composite exacerbation (CompEx) instrument.[9] The statistical analysis plan is summarized in a recent publication in the *Journal of Biopharmaceutical Statistics*.[10] The analysis plan leverages shared placebo data to optimize power for evaluating each intervention relative to placebo, in addition to analyses to determine and refine the optimal subgroup that each intervention should target. Furthermore, we will perform an early futility analysis to reduce the time committed to testing interventions that do not demonstrate efficacy on any of the 3 primary outcomes.

Network creation and governance

The NHLBI convened a scientific review group that evaluated proposals submitted in response to the RFA. Ten clinical centers (CCs) and a Data Modeling and Coordinating Center (DMCC) were chosen, and the network was formally launched in late 2017. The CCs were charged with the following tasks: to work in a collaborative manner to determine the scientific direction of the PrecISE Network; to actively implement each network-wide protocol approved by the Steering Committee (SC); to recruit and enroll severe and/or exacerbation-prone patient cohorts; to propose phenotype- and biomarker-informed adaptive clinical trials for the treatment of severe and/or exacerbation-prone asthma; to collect and report highly detailed phenotype and endotype data to answer the primary research questions of the PrecISE Network studies; and to conduct scientific analysis and interpret results. The DMCC was charged with working with CCs to develop and implement clinical protocols; conducting interim and final analyses of data; developing a statistical analysis and modeling plan to help determine the best predictive and monitoring biomarkers for use in specific patient phenotypes; developing and submitting regulatory documents to the single institutional review board (IRB) and the Food and Drug Administration (FDA); coordinating network activities and oversight by the SC and an independent, NHLBI-appointed Data and Safety Monitoring Board (DSMB); coordinating manuscript preparation; overseeing the PrecISE clinical trial budget; developing plans for drug acquisition and distribution; negotiating contracts with industry partners; and providing quality assurance.

The SC is the main governing body of PrecISE and is composed of the principal investigators (PIs) and coinvestigators of the 10 CCs and the DMCC, and the NHLBI Project Scientist. Two SC cochairs were appointed who are independent of the CCs and the DMCC to preside over SC meetings and provide guidance to the network. All major scientific decisions are determined by super-majority vote of the SC. The SC has primary responsibility for the general organization of PrecISE, finalizing clinical protocols and budgets, facilitating the conduct and monitoring of the studies, reporting study results in a timely manner, and working with the NHLBI to promote prompt dissemination of the findings. The SC also created a plan for biospecimen banking and public availability, according to NHLBI policies, during the first year of the program. The committee structure of the network is described in more detail in Section 2, and a full list of network participants is outlined in Table E1 in this article's Online Repository at www.jacionline.org.

Protocol development and implementation

Intensive protocol development and trial planning began in January 2018, and key study design decisions were made over a series of SC meetings in early 2018. The network engaged a patient advisory committee to provide guidance on key aspects of protocol design (summarized in Section 3). We selected 6 novel therapeutic agents to study initially in this precision medicine network, and additional agents to potentially enter the trial at a later time (see Table I). These include a novel biologic targeting IL-6, a medium-chain triglyceride (MCT) dietary supplement, a bacterial lysate, small-molecule antagonists of tyrosine kinases and Janus kinases, and an inhibitor of S-nitrosoglutathione reductase (GSNOR). One goal of the PrecISE Network is to identify novel biomarkers of severe asthma and response to therapy. More information about the agents selected and their biomarker-targeted subgroups is reported in Section 4.

The 3 primary outcomes in PrecISE are lung function (FEV_1), patient-reported symptoms (ACQ-6 score), and a novel surrogate for asthma exacerbations (CompEx). Section 5 reviews how these outcomes are measured and other procedures in the network.

Our network was launched at the end of 2019, but soon thereafter we put all recruitment activities on hold for 6 months due to the coronavirus disease 2019 (COVID-19) pandemic. In Section 6, we describe how we modified the protocol to reflect the new realities of conducting clinical research during the pandemic and vaccine roll-out, including low-touch strategies to maximize safety of our participants and staff. It will be important to rapidly disseminate the findings of the network to different target audiences. These efforts are coordinated and overseen by a Publications Committee, as reported in Section 7. Patient safety was a paramount concern during protocol development, with the use of novel agents not currently approved for treatment of asthma and some not approved for any indication. Our approach to safety monitoring is described in Section 8.

As the PrecISE Network ramps up subject recruitment, we look forward to implementing our innovative protocol and demonstrating the utility of precision medicine trial designs in severe asthma.

2. PrecISE COMMITTEES AND ORGANIZATIONAL STRUCTURE

The PrecISE Network consists of 10 CCs and a DMCC. Each CC comprises at least 1 PI and research team, and many involve partnerships between different institutions (see Acknowledgments for complete roster of the network). The DMCC is composed of data scientists and managers responsible for the coordination, support, and data analysis of the network.

On formation of the network, these groups undertook the monumental task of designing a novel clinical trial structure, selecting interventions and monitoring biomarkers, and implementing this trial for a complex and heterogeneous group of patients with severe and uncontrolled asthma. To this end, the PrecISE Network organized into hierarchical entities and committees that each serve a specific purpose.

Fig 2 shows the hierarchical organization of the PrecISE Network, which was informed in part by experiences in other NHLBI-supported asthma research networks.[11,12] Oversight and guidance are provided by the NHLBI and supported by a panel of experts from outside the network. The panel initially functioned as a Protocol Review Committee, and later was reconfigured as a DSMB.

The SC is composed of PIs and co-PIs from each clinical partnership and the DMCC. Two SC Chairs were appointed from the outset of the network, and are independent of the DMCC and clinical partnerships. The SC solicits progress reports from each of the clinical partnerships, as well as from the DMCC and various cores responsible for centralization of procedures, such as interpretation of spirometry, imaging, central sample processing, and biorepository. The SC also oversees the functional committees and work groups created to manage crucial components of the network.

An Executive Committee (EC) was established, which includes NHLBI program officers, DMCC investigators, the SC Chairs, and 2 representatives from among the CC PIs. The CC PIs serve 1-year rotating terms. The functions of the EC are to ensure the network remains focused on the goals of the RFA, to plan SC meeting agendas, to develop charges to and rosters of committees, and to oversee center, DMCC, and network performance and communication issues.

The organization of PrecISE committees and work groups occurred in 2 main phases, protocol design and protocol implementation, to reflect the changing needs of the network (Fig 3). PrecISE formed committees, which reported to the SC. Each clinical partnership and the DMCC was offered representation in each committee through at least 1 research team member. A complete list of committee rosters, including chair and cochairs, is contained in this article's Online Repository at www.jacionline.org.

The SC and the EC established several guiding principles to facilitate committee operations and intranetwork communication. These included using standard terminology and definitions for key concepts, committee meetings structrued around action items, timely reporting of meeting minutes, a password-protected network website where documents and meeting minutes were regularly updated, and frequent communication about committee activities by email and bimonthly SC meetings.

The following committees were established to provide foundational resources toward the overall success of the network and have remained consistent during both phases:

- Partnerships Committee: Establishes collegial relations with key industry decision makers. It obtains industry data to inform selection of interventions, and pursues agreements with companies to obtain medications and biologics for use in PrecISE at optimal cost.
- Communication Committee: Sets strategy and policies for outreach to patients with severe asthma, including engagement of community medical providers. It also directs the development of public-facing communications: public website, social media, newsletters, press releases, and so forth.

- Recruitment and Retention Committee: Works with the Communication Committee on development of promotional materials, and monitors recruitment and retention data during the course of the study, recommending adjustments as needed.
- COI and Ethics Committee: Recommends procedures to ensure that the PrecISE Study complies with National Institutes of Health regulations on financial conflict of interest. This committee conducts regular reviews of investigators' conflict of interest disclosures, and determines how to address these conflicts (eg, recusal from voting on certain topics). The committee also considers guidelines governing interactions between PrecISE investigators and pharmaceutical companies, and reviews any concerns that may require a confidentiality agreement or other actions.
- Safety Committee: Develops and establishes protocols to ensure safety of the study participants, including those related to adverse events (AEs), resource utilization, and assessment and treatment of asthma exacerbations. For each intervention, identification of intervention-specific safety exclusion criteria, additional intervention-specific safety monitoring labs, and procedures for managing abnormal results.
- Pediatrics Committee: Develops recommendations specific to the age 12- to 17-year population, to facilitate testing of biomarkers and interventions, emphasizing safety and feasibility. The committee considers the possible differing pathobiology and disease expression in adolescents, and how this may impact characterization, outcomes, and the integration with the adult population.
- Biomarker and Biospecimen Committee: Following priorities set by the SC, this committee studies the practical aspects of biomarker collection, including cost, feasibility, and any special issues related to adolescent participants. It oversees biospecimen collection, storage, and distribution for biomarker discovery. The committee helps document the procedures and develop the forms required for all biomarkers, and evaluates consent forms to ensure that biomarker data are adequately described.
- New Approaches Committee: Evaluates newly proposed interventions for possible inclusion in the PrecISE trial. Criteria include safety, feasibility, innovation, potential effectiveness, and evidence for a sensitive and specific monitoring biomarker(s). The committee also evaluates ancillary proposals for merit and feasibility.
- Publications and Presentations Committee (PPC): Promotes the generation of accurate, impactful publications and presentations that reflect the consensus of PrecISE investigators. The committee develops policies to determine authorship for PrecISE manuscripts. This is described further in Section 7.
- Biostatistics Committee: This committee reviewed biostatistical approaches during the study design phase, and advised the DMCC and the DC on different analytical approaches.

- Coordinators Committee: Provides a forum for research coordinators to collaborate across centers to ensure consistent collection of research data and to support each other toward successful recruitment, participant engagement, and in all study-related interventions.

During the design phase, the partnerships were tasked to develop an adaptive study protocol that was scientifically rigorous and statistically stable, with interventions supported by preliminary data for efficacy in severe asthma and bolstered by biomarkers predictive of efficacy or useful for monitoring of clinical outcomes. Therefore, committees for protocol development, participant/community engagement, and resource acquisition were formed.

- Protocol Development Committee: Considers and develops recommendations for phenotypes, interventions, biomarkers, and the design approach, while considering safety and cost.
- The Protocol Development Committee encompassed multiple working groups: The *Definitions* Working Group established the rigorous definitions for severe asthma, exacerbation, and end points.[13] The *Protocol Design and Analysis* Working Group created models from the protocol to determine statistical power and established statistical methods for data analysis.[10] The *Protocol Elements Committee* developed visit structures, inclusion and exclusion criteria, and descriptive standards for protocol compliance and participant discontinuation. Following priorities set by the SC, an *Intervention Working Group* was created for each of the interventions selected as possibly feasible and efficacious in the study population. Each working group developed a proposal for dosing, monitoring, and acquisition of study drug.
- Participant Advisory Committee: Inherent to a complex clinical trial for treatment of a severe disease is participant burden. The Participant Advisory Committee held multiple participant and community engagement sessions in which patients with severe asthma, and their family members, were asked to provide feedback on the proposed protocol, procedures, interventions, and outcomes. This valuable feedback was used in all aspects of PrecISE Study development, as described in the following section.
- Resource Acquisition Committee: This committee works on forms development, equipment acquisition, and interfacing with site study coordinators and PrecISE central reading centers and cores.
- In the implementation phase, committees reflected the remaining tasks necessary for the study to begin enrollment.
- Adaptation and Design Committee: Formed in part as a response to input from the external Protocol Review Committee, this committee examines issues such as how new interventions will be prioritized and implemented, the need for a dynamic consent and reconsent process, and potential sources of participant bias.
- Quality Control: Performs quarterly reviews of quality control measures including data queries, protocol violations, data completeness, biospecimen

quality, and quality measures provided by the cores and working groups. Provides recommendations for process improvements and retraining to the SC.

The Protocol Implementation Committee was formed to replace the Protocol Development Committee. Like its predecessor, the Protocol Implementation Committee oversaw multiple working groups (see Table E2 in this article's Online Repository at www.jacionline.org). The success of this complex clinical research network has required an organizational and leadership structure that emphasizes accountability, teamwork, and adaptability to different stages of research work. The PrecISE Network will again reorganize committees if necessary, to meet the needs of future research stages. The committees and work groups supporting PrecISE will ensure its success.

3. METHODS AND RESULTS OF ENGAGING A PARTICIPANT ADVISORY COMMITTEE FOR PrecISE (COMMITTEE CHAIRS, DR LYNN GERALD, UNIVERSITY OF ARIZONA, KIM ERWIN, UNIVERSITY OF ILLINOIS AT CHICAGO, AND DR JERRY KRISHNAN, UNIVERSITY OF ILLINOIS AT CHICAGO)

Rationale and proposed role for the Participant Advisory Committee

There is relatively little published information about the methods and results of stakeholder engagement in clinical trials to support discovery science (eg, phase 1, 2, or 3 clinical trials). Here, we describe the methods and results of engaging adolescents and adults with severe asthma and their caregivers to inform the design of the PrecISE clinical trial.

The PrecISE SC recommended the development of a Participant Advisory Committee (PAC) to solicit feedback among adolescents (and their caregivers) and adults with severe asthma in 5 areas: (1) acceptability of clinical trials among adolescents, their caregivers, and adults with severe asthma; (2) study processes, such as randomizations, placebos, and washouts; (3) study procedures, such as schedules, tests, and incentives; (4) expected participant activities between visits, specifically medication tracking and logging; and (5) proposed treatments, including pathways and blinding. The PAC was coled by 3 PrecISE investigators (Jerry Krishnan, Lynne Gerald, and Rajesh Kumar) and an expert in human-centered design (Kim Erwin).

Represented groups and methods of recruitment

A 7-month scope of work was approved by the PrecISE SC that included 3 in-person workshops in Chicago, Tucson, and Winston-Salem. These locations were selected for their combined diversity of patient populations (White, LatinX, Black), settings (urban, suburban, rural), and geography (Midwest, Southwest, Southeast). PrecISE investigators were invited to nominate individuals who were 12 to 70 years old with clinically diagnosed severe asthma; caregivers of adolescents (age 12–17 years) with severe asthma were also invited. Adults were invited to participate in in-person half-day workshops, and adolescents were invited to participate in individual interviews with their caregivers to ensure the trial fit the family, not just the patient.

Structure of the PAC

Workshop participants included 10 Black participants, 8 White participants, 1 White caregiver, and 1 LatinX caregiver across the college-age to retirement life stages.

Approaches to the generation of data and PAC input

Workshops were conducted using 3 large-format (3 × 5 feet) information graphics, designed to help participants easily understand and discuss study goals and its precision medicine model; the participant enrollment experience from data collection through randomization; and the participant visit schedule, treatments, and specific procedures during the study. Participants were given markers and invited to annotate printouts as each topic was discussed. Feedback was recorded on the printouts so everyone could see the accumulated viewpoints and recommendations (Fig 4).

Five adolescents (2 Black, 1 White, and 2 LatinX) and their caregivers were interviewed. Adolescent interviews used projective images (images of different emotions) and the information graphics. Adolescents and their caregivers were asked to pick 2 images that best represented their feelings about coping with severe asthma. Together these supports were used to elicit perceptions of the fit, relevance, and feasibility of the proposed study, especially in light of high school demands and challenges of being a young person with a severe chronic disease. All interviews were conducted with the caregiver present and were recorded and transcribed. The study procedures were reviewed by an IRB and determined to be exempt (University of Illinois at Chicago IRB, 2018-0938). Written permission to photograph PAC participants during the sessions was obtained.

Issues brought forward by the PAC and their resolution

PAC participants proposed 19 key recommendations across the 5 themes (Table II). Participants indicated that the study was important to people with severe asthma and were broadly supportive of an adaptive trial design that could produce results promoting “personalized” disease treatment. Many described being traumatized by their illness, frustrated by a lack of effective treatment options and repeated hospitalizations, losing their jobs, relationships, or putting school on hold for months and years. As a result, the PAC expressed enthusiasm for PrecISE’s strategy of testing different interventions over time, rather than a single intervention, to provide an opportunity to understand the risks and benefits in individual study participants. PAC participants also offered to assist with recruitment of trial participants and to provide ongoing advice to study investigators, once the study was open for enrollment.

Adults highlighted study logistics, rather than the treatments or procedures, as needing accommodation. They requested assistance that could help them complete the study, such as flexibility in scheduling, extra supports to help integrate treatments into their daily routines, and the ability to switch sites (snowbirds and college-enrolled) as needed over the long duration of the study. Adolescents and caregivers expressed more caution; parents noted they are protective of their children and want them back on track, succeeding in school and paving a path for their future. More time away from school, family, and friends for study visits was cited as a significant concern. One parent said, “I just need to know what the

actual responsibility is for our family to be part of a study in terms of doctors' appointments. He's in 8th grade right now, he's already missed a third of the school year on doctors' appointments." Parents also asked for more flexible follow-up procedures (eg, at-home spirometry and blood panels performed locally) that could minimize the inconvenience and travel time to sites that are sometimes hours from home. Adolescents concurred, expressing guilt at the demands their illness had already placed on their families, and gratitude for the partnership with their parents.

Ongoing involvement of the PAC in PrecISE

The PrecISE PAC strongly supported the core study questions and noted the answers were crucial to a better future for those with asthma. One participant commented, "I would like to participate because even if participating doesn't help me then it can help other kids and their families in the future." An adaptive clinical trial design was perceived as necessary to more effectively address the unique needs of people with severe asthma. The PAC also expressed interest in supporting clinical trial participation as a way of giving back and preventing others from struggling as they had.

Participant engagement is both common and de rigueur for delivery science.[14–18] It is less common in discovery science where the focus is on investigator-defined outcomes and mechanistic studies. In recent years, the average length of a clinical trial increased by 70% and the average number of study procedures increased by 65%, with a concomitant 21% drop in enrollment rates and a 30% drop in retention.[19,20] A recent systematic review indicated that patient engagement can increase study enrollment rates and aid researchers in designing study protocols to increase retention.[16]

Incorporating PAC feedback to improve the research experience and enhance recruitment and retention efforts is a challenge in multisite clinical trials, particularly those focused on discovery science. Barriers among discovery science investigators include a lack of familiarity with qualitative methods. Clinical trialists are often not familiar with the standard qualitative principle of saturation, the criterion for determining sample size.[20] Reaching saturation in qualitative research means that no new information is being obtained. Often, this occurs at much smaller sample sizes than those clinical trialists are used to seeing, which leads to questions about the generalizability or usefulness of PAC input.[19] Another barrier to incorporating PACs in discovery science is limited experience in integrating feedback from individuals with the target condition. Once information is gained from the PAC, researchers must take specific steps to revise protocols to account for this feedback and sometimes these steps are hard to identify. Complexity of scheduling early and continuous engagement activities between nonscientific stakeholders and study investigators can also be a barrier to working with PACs. Individuals with severe asthma may not be able to convene on-demand due to personal commitments, but investigators need to move quickly with establishing scientific protocols to ensure clinical trial milestones are met. Finally, we lack rigorous evidence about how participant engagement can translate into improved study performance (eg, recruitment and retention) in discovery science clinical trials.

To address these barriers, we suggest (1) establishing a clear mechanism and time points in protocol development to respond to PAC-proposed modifications; (2) developing training

curricula about research that is accessible to nonscientific stakeholders; and (3) integrating study coordinators when interpreting input from a PAC, because study coordinators are participant-facing and would be particularly well suited to incorporating their suggestions during study implementation. PAC recommendations do not have to be implemented all at once and can often be incorporated over time, especially when conditions change (such as during the COVID pandemic). Furthermore, using PACs throughout the study process and not just for initial consultation is likely to further improve clinical trial adherence and interest for participants. A framework for such continuous patient engagement has been proposed by Mullins et al[17] where patients are engaged in every step of research from topic solicitation to dissemination. Clinical trials should consider having a Participant Engagement Core similar to other central cores (as in Fig 2).

The PAC works closely with the Recruitment and Retention Committee to implement strategies to enhance subject recruitment in general, and minorities and adolescents in particular.[21] Some of the steps taken, based in part on PAC recommendations, include (1) using flexible scheduling including evening and weekend appointments, (2) allowing participants to switch sites if they move (eg, graduating high school seniors going to college in another city, see below), (3) combining study appointments with clinical appointments, (4) reimbursing subjects for transportation to the site, and (5) using surveys/procedures that can be done at home to shorten face-to-face visits. We will continue to engage the PAC during later stages of trial implementation and results reporting in the PrecISE Network as resources permit.

In conclusion, the PrecISE PAC experience suggests that individuals with severe asthma are highly supportive of the overall goals of the PrecISE adaptive clinical trial design and that engaging individuals with the target condition of interest can be used to inform clinical trial enrollment and retention procedures. Studies evaluating the impact of integrating the recommendations of individuals with the condition of interest, such as asthma, in discovery science clinical trials on recruitment and retention are needed.

4. STUDY MEDICATIONS IN PrecISE

The major goals of PrecISE are 2-fold: (1) to identify novel interventions for severe asthma and (2) to optimize biomarkers of response to therapy for each intervention. Therefore, one of the first tasks of the network was to select and prioritize a list of interventions. Each participating center proposed 1 or more interventions to the SC. The proposals included preliminary data for efficacy in severe asthma, safety considerations for the population with severe asthma (including adolescents), feasibility of dosing and placebo matching, acceptability to the participant, logistic challenges for drug acquisition, and strength of predictive and monitoring biomarkers. Predictive biomarkers are defined as those that are measured before treatment and used to predict response to therapy, whereas monitoring biomarkers are measured serially over time during treatment periods as indicators of response. Using this information, the SC identified 6 priority interventions (see Table I and below). Six intervention working groups were formed that identified industry contacts and developed intervention-specific protocols and procedures. An important advantage of our master protocol and adaptive platform trial design is that interventions can enter the

study when they become available, and leave the study at different times and for different reasons (eg, stopping early for futility or graduating for further study).[9]

Clazakizumab (anti–IL-6) (Working Group Chairs: Dr Michael Peters and Dr John Fahy, University of California San Francisco)

Rationale for selection.—The prominence of older age and obesity among the phenotypic features of severe asthma[5,22,23] raises the possibility that the systemic inflammation associated with aging, obesity, and metabolic dysfunction may have effects in the airway to worsen asthma. Low-grade systemic inflammation occurs in a subset of obese patients,[24] because adipocytes and inflammatory macrophages in adipose tissue secrete proinflammatory cytokines such as IL-6.[25] Although low-grade systemic inflammation is associated with insulin resistance, atherosclerosis, type 2 diabetes, and hypertension, the role of systemic inflammation and metabolic dysfunction as risk factors for severe asthma is poorly understood. Two recent studies of plasma IL-6 levels in the Severe Asthma Research Program-3 (SARP-3) provide evidence that systemic IL-6 inflammation commonly present in older patients with metabolic dysfunction could impair lung health. SARP-3 is a longitudinal cohort study that includes participant characterization at baseline and annually for 3 years and longer. In a cross-sectional study focusing on baseline data, increased plasma IL-6 levels (but not sputum IL-6 levels) were strongly associated with features of metabolic dysfunction (obesity, hypertension, and diabetes) and features of severe asthma (lower lung function and history of asthma exacerbations).[26] In a subsequent study focused on prospectively captured 3-year asthma exacerbation rates, participants with recurrent exacerbations (“exacerbation-prone asthma”) were characterized by increased body mass index, higher prevalence of hypertension and diabetes, and higher levels of plasma IL-6. Furthermore, each 1-pg/mL increase in baseline plasma IL-6 levels increased the incident rate ratio for exacerbation risk by 10%.[27] Together, these findings lead us to hypothesize that IL-6–related systemic inflammation originating outside the lung impairs lung function from the “outside in.”[28] Targeting the IL-6 axis has proven to be helpful in chronic inflammatory diseases such as rheumatoid arthritis, giant cell arteritis, psoriatic arthritis, and cardiovascular disease, and we propose to test here whether it is helpful in severe asthma as well. Therefore, we hypothesize that inhibiting IL-6 will improve asthma control and reduce exacerbations in patients with severe asthma.

The link between systemic IL-6 inflammation, obesity, and asthma morbidity may be mediated by IL-6− driven immune dysfunction that weakens airway host defense. A sputum cell gene expression signature for $CD8^+$ T cells is decreased in obese patients with asthma,[29] a finding consistent with known impairments of $CD8^+$ T cells (and natural killer cells) by obesity and systemic IL-6 inflammation.[30,31] Such impairments in $CD8^+$ T cells and natural killer cells could weaken airway defense against viral infection. Relevant here is the clinical trial data showing that inhibiting the IL-1/IL-6 axis in patients with high plasma IL-6 levels decreases the risk of developing lung cancer.[32] This anticancer effect may be explained by the ability of anti–IL-6 treatment to restore the ability of cytotoxic T cells to detect and eliminate malignant cells.[30,31] This raises the possibility that anti–IL-6 treatment may also restore natural killer–cell and $CD8^+$ T-cell function to normalize antiviral airway defenses and decrease virus-induced asthma exacerbations.

Another plausible mechanism of IL-6–mediated asthma morbidity is the role of IL-6 in propagating T_H17 cells and IL-17–associated inflammation.[33] IL-6 is critical for the differentiation of naive $CD4^1$ T cells into T_H17 cells.[34] Furthermore, a recently discovered genetic polymorphism in the IL-4 receptor alpha chain promotes conversion of induced regulatory T (Treg) cells toward T_H (T_H17) cells in mice and humans with asthma.[35] This skewing toward T_H17 is promoted by IL-6, mediated by Notch 4, and inhibiting IL-6 with anti–IL-6 antibodies prevented T_H17-mediated airway inflammation in mice.[35,36] In human asthma, treatment with the anti–IL-6 medication tocilizumab in 2 children suppressed T_H2/T_H17 responses, improved asthma symptoms,[37] and reduced NOTCH4 expression on Treg cells.[36]

Pharmacology.—Clazakizumab is a human recombinant mAb that binds to the IL-6 ligand and blocks binding to its soluble and membrane-bound IL-6 receptors. Clazakizumab will be administered subcutaneously at a dose of 12.5 mg every 4 weeks. This dose was selected to maximize clinical efficacy and minimize the risk of AEs, but dose modification will be available as discussed in the Safety subsection. A reduction in serum C-reactive protein (CRP) levels occurs as a result of IL-6 signal blockage.[38] Thus, decreases in serum CRP levels indicate effective blockade of the IL-6 axis. Clazakizumab administered at a dose of 12.5 mg subcutaneously every 4 weeks is effective at suppressing blood CRP levels would indicate appropriate inhibition of systemic IL-6 inflammation at this dose. Lower AE rates have been seen with lower doses of clazakizumab.[39,40] Clazakizumab pharmacokinetics has been studied in patients with rheumatoid arthritis and healthy control subjects. In a phase 1 study of healthy male subjects, the mean half-life of clazakizumab ranged between 31.1 and 33.6 days after subcutaneous administration, and across studied doses of 25 mg to 200 mg, the pharmacokinetics was observed to be linear. Because of the relatively long half-life of clazakizumab, the washout period for the clazakizumab arm has been extended from 8 weeks to 16 weeks. The cumulative washout will be 20 weeks because the final dose of clazakizumab is administered 4 weeks before the end of the study. The 20-week washout is equivalent to 5 half-lives and will ensure that plasma clazakizumab concentrations drop to less than 94% of the starting dose. As expected for a humanized mAb, the volume of distribution (V_d) of clazakizumab is small (<6000 mL) and suggests little distribution from the extracellular fluid to tissue.

Potential predictive and monitoring biomarkers.—The main predictive biomarker for the anti–IL-6 intervention is plasma level of IL-6. IL-6 is produced by macrophages and activated T cells. IL-6 can be measured in plasma or serum samples, and a Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory test is available from PPD Laboratories. Recently, the NHLBI SARP-3 study found that approximately 33% of participants with severe asthma had increased plasma IL-6 levels (>3.1 pg/mL). The 3.1-pg/mL cutoff was derived from a reference value representing the upper 95th centile of IL-6 levels in plasma from healthy control subjects (n = 95). Participants with “IL-6 high” asthma were characterized by worse asthma symptoms, decreased lung function, and increased asthma exacerbation rates when compared with “IL-6 low” asthma participants.[26]

IL-6 stimulates hepatocytes to produce and secrete CRP and other acute-phase proteins, such as serum amyloid A, into the systemic circulation.[41] We will measure CRP and serum amyloid A levels as surrogate markers of IL-6 activation. In particular, we will use the high-sensitivity CRP test as the primary response/pharmacodynamic biomarker of systemic IL-6 activity; we will explore its utility as an alternative to plasma IL-6 as a secondary *predictive* biomarker to identify patients responsive to clazakizumab.

Safety monitoring considerations.—Clazakizumab is a human recombinant mAb that binds to IL-6, and clinical trials of clazakizumab in rheumatoid arthritis and psoriatic arthritis have shown clinical efficacy.[39,40] Sarilumab and tocilizumab are mAbs that bind to the IL-6 receptor, and these drugs are both FDA-approved to treat rheumatoid arthritis. Tocilizumab is also FDA-approved for the treatment of giant cell arteritis, polyarticular juvenile idiopathic arthritis, and cytokine release syndrome.[42–46] The risks of inhibiting IL-6 or IL-6R are similar and include injection-site reactions, more frequent infections, liver dysfunction, neutropenia and thrombocytopenia, hypercholesterolemia and hypertriglyceridemia, bowel perforation, and (very rarely) demyelination. To mitigate the risk of liver dysfunction and cell count dyscrasia, a safety lab monitoring protocol was developed for dose reductions when baseline or monitoring safety lab thresholds were met (see Table E3 in this article's Online Repository at www.jacionline.org). Subjects who have a dose adjustment to the lower 6.25-mg dose will remain at the 6.25-mg dose until the end of the intervention unless the subject meets criteria for discontinuation of the drug (ie, diverticulitis, triglycerides >1000 mg/dL, or an opportunistic infection). If a subject meets criteria for discontinuation of the drug, they will not be given additional drug doses, but they will remain in the trial and complete all procedures. To mitigate the risk of serious infections, we elected to exclude patients with a history of diseases associated with immunosuppression and/or individuals with known infections such as tuberculosis, HIV, and hepatitis. Patients taking other immunosuppressive medications were also excluded from this trial. Finally, the relatively short trial length of 16 weeks will minimize the exposure period and infection risk but allow sufficient time to determine clinical efficacy.

Breathe better diet: MCT supplementation (Working Group Chair: Dr Serpil Erzurum, Cleveland Clinic)

Rationale for selection.—Altered cellular metabolism plays a role in asthma origins through diverse effects on immune cell differentiation and functions[47,48] including a strong link between asthma and metabolic syndrome,[49–51] high prevalence of obesity in patients with asthma, and obesity as a risk factor for atopic and nonatopic asthma.[49–53]

The airway inflammation of asthma is typified by high levels of T_H2 cytokines, nitric oxide (NO), and reactive oxygen species, all of which are modulated by bioenergetic pathways.[54,55] The high fractional exhaled nitric oxide (FENO) in asthma is generated by inducible NO Synthase, which catalyzes conversion of arginine to NO and citrulline.[56–58] High NO in asthma is associated with inflammatory injury,[57,58] but metabolism of arginine may also contribute to asthma through pathways other than generation of NO. Arginine levels in asthmatic airways are higher than in healthy controls.[56] Cells synthesize arginine endogenously via argininosuccinate synthetase, which uses citrulline and aspartate as

substrates to form argininosuccinate that is subsequently cleaved by argininosuccinate lyase to generate arginine (Fig 2). In addition to higher inducible NO Synthase and arginine levels, arginase 2, which catabolizes arginine to ornithine, is increased in asthma.[59] The ornithine generated by arginase 2 gives rise to glutamate and then α-ketoglutarate, which enters the tricarboxylic acid (TCA) cycle (Fig 5). Thus, arginine metabolism is closely linked to the TCA cycle flux in the mitochondria.[59,60] In addition to energy production, mitochondria are an important source for reactive oxygen species generation in inflammation.[61–63]

Mitochondrial function is central in regulating metabolism and susceptibility to allergic and immunologic diseases.[59,64,65] The arginine-citrulline-NO cycle is linked to the TCA cycle,[61] and there is a high arginine metabolic subphenotype of asthma.[66,67] Mitochondrial provision of TCA cycle intermediates for oxidative metabolism may have important consequences on signal transducers of airway inflammation. Greater TCA cycle flux dampens proinflammatory signal transduction events that are central to asthma origins, and serves as a brake on T_H2 inflammation, suggesting potential beneficial effects to suppress airway inflammation in asthma.[59,60,67]

Studies suggest that patients with asthma have systemic changes in bioenergetics and mitochondrial metabolism.[52,59,60,68–72] Changes in mitochondria appearance and function are present in the ovalbumin allergen-murine experimental asthma model,[65,73] and linked to asthma features, including hyperresponsiveness and T_H2 inflammation.[74] Picado et al[52] showed that individuals with mild asthma are metabolically more efficient as compared with healthy controls. The codependency of bioenergetics and inflammation pathways provides an opportunity to target bioenergetics in treatment of asthma.

Dietary composition regulates metabolism and cellular processes that produce oxidants and cause inflammation. Studies have shown that inflammation can be mitigated by caloric restriction.[75] Intermittent caloric restriction improves metabolism, decreases inflammation, increases longevity, and decreases risk of diabetes, cancer, and cardiovascular disease, independent of weight loss.[76,77] Studies suggest that beneficial effects of caloric restriction on immune function can be mimicked by supplementing the diet with MCTs.[48,78]
In addition to glucose/pyruvate metabolism by mitochondria, lipids are catabolized by mitochondrial beta oxidation. MCTs as compared with long-chain triglycerides cross the mitochondrial membrane independently of the acylcarnitine transfer system, leading to an increase in energy sources and preferential metabolic utilization. MCT interventions are known to change mitochondrial energy metabolism as compared with either long-chain triglycerides or carbohydrates and afford benefits for brain[79] and cardiovascular health.[80] This intervention will test whether a specific MCT intervention may benefit clinical outcomes in patients with asthma.

Pharmacology.—The study intervention is a daily supplement of a unique and specific MCT formulation (Vitaflo, Alexandria, Va) or placebo. The MCT and placebo are provided in sachets and contain 2 g protein, 10 g fat, and 98 Kcals. The active supplement contains a proprietary formulation of MCTs designed to reduce airway inflammation. In the placebo supplement, MCTs will be replaced with polyunsaturated and monounsaturated fats derived from canola oil. The supplement dose is standardized so that the MCT or the placebo fats

provide approximately 15% of a participant's total dietary caloric intake. Total dietary intake is calculated on the basis of participant's dietary intake required to maintain body weight at their daily kilocalorie expenditure. Daily kilocalorie expenditure is calculated from resting energy expenditure obtained by the Mifflin-St Jeor equations[81] multiplied by a sedentary physical activity factor of 1.2. Dietary intake is further validated by a standardized, electronic dietary recall method (Automated Self-Administered 24-hour Recall, National Cancer Institute, Bethesda, Md).[82] The supplements are provided in powder form and can be mixed in various foods and beverages. Participants are instructed on daily supplement consumption by trained PrecISE Study staff, mixing and recipe handouts, and receive oversight from a registered dietitian. Participants with a body mass index of 40 kg/m^2 or greater are excluded from this intervention because of suboptimal dosing. Participants with diabetes, milk allergy, and coconut allergy are also excluded.

Potential predictive and monitoring biomarkers.—The arginine-citrulline-NO cycle is linked to the TCA cycle,[59] and there is a high arginine metabolic subphenotype of asthma.[66,67] High levels of metabolism are required to sustain arginine availability in asthma, and this metabolic flux is associated with dampening inflammation.[59] Greater arginine flux thus preserves cellular respiration and suppresses pathological signaling events that promote inflammation in asthma. We propose to use FENO as a biomarker to predict greater benefits of treatment with MCT. FENO is an exhaled biomarker that is easily measured, readily available, and able to be obtained rapidly. Preliminary data based on a similar MCT product in a small clinical early-phase study suggests that responders to MCT with FENO more than 15 parts per billion (ppb) may be more likely to respond to MCT than those with lower FENO: therefore, FENO more than 15 ppb is the primary predictive biomarker. It is unknown whether FENO might change with MCT supplementation.

Safety monitoring considerations.—MCTs are safe, but some people experience side effects, which include diarrhea, nausea, stomach discomfort, and intestinal gas. To minimize patient burden and discomfort, a dose-escalation protocol is used to reduce the risk of gastrointestinal side effects. The goal is to provide a small initial exposure to the nutritional supplement, monitor side effects, and dose escalate to reach the prescribed dose by the 2-week time point. A day-by-day guideline to reach the full supplement prescription, starting with a low dose and slowly building to the full dose, will be provided to participants. Stage 1 dosing starts with a ½ sachet (equivalent to 5 g MCT or placebo), once per day, ramping up incrementally to achieve the full dose (adjusted for each participant; typically 3–4 sachets, or 30–40 g MCTor placebo fats per day) within 2 weeks. Participants who do not reach their prescribed dose by the 2-week mark will receive more intensive nutritional consultation and reevaluation at that time.

Imatinib (C-kit inhibitor) (Working Group Chair: Dr Elliot Israel, Harvard University)

Rationale for selection.—Mast cells (MCs) are powerful, long-lived, tissue-dwelling, hematopoietic effector cells that have been implicated in the pathobiology of asthma.[83] MCs can persist in the face of steroid therapy, and MC burden in the airway smooth muscle correlates with airway responsiveness and asthma disease severity.[84–86] Tryptase, an MC granule–associated protease, is a marker of MC activation when detected in extracellular

fluids.[87] Tryptase levels in bronchoalveolar lavage fluid of patients with difficult-to-control asthma exceed those in well-controlled asthma.[88,89]

Stem cell factor and its receptor, the c-KIT tyrosine kinase receptor, are essential for normal MC development and survival in tissues.[90,91] Soluble stem cell factor levels are elevated in the serum of patients with asthma and correlate with asthma severity.[92,93] c-KIT inhibitors, such as imatinib, inhibit the tyrosine kinase activity of wild-type c-KIT[94] and as a consequence markedly reduce bone marrow MC numbers and serum tryptase levels in patients with chronic myeloid leukemia,[95] and reduce serum tryptase in subjects with pulmonary hypertension.[96] In a murine chronic allergen exposure model characterized by peribronchial thickening and fibrosis, imatinib at 5 mg/kg reduced peribronchial eosinophils by more than 50% and reduced hydroxyproline levels by more than two-third, and almost completely ablated the increase in airway resistance in response to methacholine compared with controls.[97]

Cahill et al[98] previously conducted a randomized, double-blind, placebo-controlled 24-week phase 2 trial in patients with severe asthma to evaluate the effects of c-KIT inhibition with imatinib on airway hyperresponsiveness. Sixty-two patients were randomized to imatinib or placebo, and the primary outcome was change in airway responsiveness. Treatment with imatinib reduced levels of serum tryptase (baseline levels = 4.81 ng/mL), a marker of MC activation, to a greater extent than did placebo (43% vs 12% reduction; P=.015; Fig 6). Imatinib decreased airway responsiveness to methacholine at 6 months compared with placebo; specifically, the methacholine PC_{20} increased by a mean of 1.73 ± 0.60 doubling doses in the imatinib group, compared with 1.07 ± 0.60 doubling doses in the placebo group (P =.048). In addition, FEV_1 improved in the imatinib group as compared with placebo, and this improvement correlated with the decline in airway MC numbers.

Participants treated with imatinib also experienced numerically (but not statistically significantly) fewer exacerbations, reduced airway wall thickness on computed tomography (CT) scan, higher peak flows, better asthma control (as determined by Asthma Control Questionnaire, Asthma Quality of Life Questionnaire, Asthma Symptom Utility Index), and improvements in both AM and PM peak expiratory flow compared with placebo. On the basis of findings of this study, we designed the imatinib arm of the PrecISE trial with the goal of optimizing patient responder selection based on biomarkers, and testing for important efficacy outcomes, as described below.

Pharmacology of imatinib.—Imatinib was originally approved for the treatment of chronic myelogenous leukemia, where it inhibits the oncogenic BCR-ABL tyrosine kinase receptor by targeting the ATP-binding site.[94] In chronic myelogenous leukemia, the BCR-ABL tyrosine kinase arises because of translocation and fusion between the genes encoding BCR and ABL, resulting in the Philadelphia chromosome. The likely target of imatinib in asthma is c-KIT, but it should be noted that imatinib also inhibits tyrosine kinase receptors including the platelet-derived growth factor receptor.[99] The half-life of imatinib is approximately 18 hours following oral administration in healthy volunteers, which makes it appropriate for once-daily dosing. The increase in mean imatinib plasma concentration with increasing dosing is linear and dose proportional in the 25- to 1000-mg dosing range.

A change in the kinetics of imatinib is not seen with repeated dosing. More than 12,000 people have been exposed to imatinib. Dosing for PrecISE is 200 mg per day, by mouth, for 2 weeks followed by 400 mg once daily, consistent with previous dosing in the study by Cahill et al.[98]

Potential predictive and monitoring biomarkers.—In the previous phase 2 trial,[98] improvements in PC_{20} were negatively correlated with peripheral blood eosinophil counts ($r^2 = 0.22$; $P < .05$). Furthermore, improvement in FEV_1 was correlated with bronchoalveolar lavage neutrophil counts ($r^2 = 0.44$; $P < .01$). Participants with less than 300 eosinophils/μL were more likely to experience improvements in airway hyperresponsiveness, with 84% sensitivity and a 75% specificity.[98] The finding that c-KIT inhibition was most effective in patients with more neutrophilic and less eosinophilic inflammation suggests that MCs may be contributing to non–type 2 (ie, type 2–low) inflammatory pathways in these patients treated with high-dose inhaled corticosteroid (ICS), where type 2 inflammation may be suppressed. Therefore, the primary predictive biomarker for imatinib is low peripheral blood eosinophil counts (<300/μL), which is a clinically relevant cutoff used to distinguish patients responsive to anti–type 2 biological agents.

Additional predictive biomarkers will also be measured. *S*erum tryptase has been used as a marker of MC activity and will be a secondary predictive biomarker. In the previous phase 2 trial, a 28.5% decline in serum tryptase had an 82% sensitivity and a 71% specificity of identifying participants with improvements in FEV_1 with an area under the receiver-operating characteristic curve of 0.77.[98] In addition, as noted above, improvements in FEV_1 correlated with bronchoalveolar lavage neutrophil counts. Although bronchoalveolar lavage will not be measured in this trial, we will propose assessing whether sputum neutrophils can serve as a potential surrogate of airway neutrophilic inflammation[100] and serve to identify a subgroup of patients that may be more responsive to imatinib. We will also test for the ability of the following assays to predict efficacy responses to imatinib: sputum tryptase, urinary prostaglandin D2 metabolite, sputum MC gene expression, and flow cytometry of peripheral blood T-cell subsets and of MC precursors. We propose to assess whether changes in serum tryptase, sputum MC gene expression, peripheral blood T-cell subsets, and/or urinary prostaglandin D2 metabolite correlate with improvements in clinical asthma outcomes as monitoring biomarkers.

Safety monitoring considerations.—The most common side effect (>10% of patients) from imatinib observed in humans is nausea. Leukopenia can occur (between 1% and 10% of patients), and hepatoxicity occurs rarely (<1% of patients). Patients participating in nononcologic trials have tolerated the medication well.[101] Hypophosphatemia occurred in 19% of the patients in the phase 2 trial in severe asthma.[98] Specific to imatinib, we will monitor serum phosphate, peripheral blood neutrophil and platelet counts, and liver function tests through safety interim labs. Because of the frequency of hypophosphatemia, we will provide phosphate supplementation as needed and a placebo phosphate preparation on a proportional basis to those randomized to placebo, so as to maintain blinding. We will decrease the imatinib dose (active or placebo) by half if elevations in serum aspartate transaminase, alanine aminotransferase, or total bilirubin, or decreases in either neutrophil

or platelet counts, occur, with a sham dose adjustment procedure implemented for placebo participants. Should any of these side effects occur and fail to normalize after changing to a half dose, we will discontinue imatinib administrations.

Broncho-Vaxom (Working Group Chair: Dr Fernando Martinez, University of Arizona)

Rationale.—A large body of recent evidence suggests that microbes present in the gut and airways and their products play a role in the inception and severity of asthma.[102] In children, a specific compositional set of the gut microbiota present during the first year of life was shown to increase the risk for developing asthma and atopy by the age of 6 years.[103] Sterile fecal water from children carrying this set shifted T cells *in vitro* away from $CD4^+CD25^+Foxp3^+$ Treg cells and in favor of T2-type T cells. Moreover, 12,13-dihydroxy-9Z-octadecenoic acid, a cytochrome P450–derived linoleic acid metabolite, which was more abundant in the gut microbiota compositional set that predisposed for asthma, reproduced this effect.[103] These results suggest that in early childhood-onset asthma, which is the most common form of the disease,[104] the composition of the gut microbiota plays a critical role, and that this role seems to be at last partially mediated not directly by the live bacteria themselves, but by their metabolic products.

These studies have raised the possibility that medicines consisting of specific intestinal microbiota and their metabolites may play a role in asthma therapeutics, and drug development efforts are ongoing to achieve that goal. Alternatively, experimental and clinical studies have explored the potential role of existing products consisting of lyophilates of respiratory bacteria in the treatment of asthma symptoms. These products have been used empirically for decades in Europe as immune modulators for the prevention of respiratory illnesses,[105] but are not available in the United States.

One of these products, Broncho-Vaxom, has as active ingredient an endotoxin-low, lyophilized lysed extract of 21 bacterial strains from 5 pathogenic genera: Haemophilus, Streptococcus, Klebsiella, Staphylococcus, and Moraxella. Broncho-Vaxom was used empirically for the prevention of recurrent respiratory tract infections (RTIs). A recent, systematic meta-analysis of 8 clinical trials found that in children treated with Broncho-Vaxom (n = 435), 32% had recurrent RTIs versus 58.2% in placebo-treated patients (n = 416; $P < .001$).[106] The author concluded that Broncho-Vaxom was significantly and consistently effective in preventing recurrent RTIs in children and that the data suggested that the effect was greater in patients at increased risk of recurrent RTIs. The clinical efficacy of Broncho-Vaxom in the prevention of acute virus–induced wheezing in young children aged 1 to 6 years with recurrent wheezing lower respiratory illness was evaluated in an investigator-initiated randomized, double-blind, placebo-controlled, 12-month study.[107] Children received Broncho-Vaxom or placebo (3.5 mg/d) for 10 days each month for 3 consecutive months. The results showed that the number of wheezing episodes was reduced by 38% and the duration of these episodes was reduced by 2 days in children treated with Broncho-Vaxom compared with those who received placebo ($P \leq .001$).

Of greater relevance for severe asthma, a recent randomized, double-blind, placebo-controlled, parallel-group study was performed in 6- to 16-year-old patients (n = 152) with allergic asthma who received orally a 12-week treatment of either placebo or a

bacterial lysate very similar in composition to Broncho-Vaxom.[108] At baseline, all children were treated with either ICS + long-acting β-agonist (56%) or ICS (44%) and had mean Asthma Control Test scores of 17.5, indicating uncontrolled asthma. Although the primary outcome (asthma control level as assessed by the Asthma Control Test/Child-Asthma Control Test score) did not reach statistical significance, the mean number of asthma exacerbations was 63% lower in children treated with lysate tablet than with placebo at week 12 ($P = .009$). Exacerbations were defined as moderate if they required a transient increase in ICS/β2-agonist/anticholinergic use for 2 or more days, or an emergency room visit but without prescription of systemic glucocorticoids (96%); or severe if requiring hospitalization or emergency room visit and systemic glucocorticoids to be prescribed or systemic glucocorticoids (oral or parenteral) to be prescribed for 3 or more days. This definition overlaps extensively with that of an "episode" ascertained by use of the CompEx algorithm,[109] which is proposed as 1 of 3 primary outcomes in PrecISE.

No asthma studies are available in adults. However, Broncho-Vaxom has been tested in placebo-controlled trials of chronic obstructive pulmonary disease, and a recent meta-analysis described the results of 4 randomized controlled trials with 1200 patients.[110] Broncho-Vaxom was associated with a 20% decrease in the rate of chronic obstructive pulmonary disease exacerbations as compared with placebo. These results, added to those for childhood asthma, support the possibility that Broncho-Vaxom may be effective in preventing accurate exacerbations of chronic respiratory illness.

Experimental studies provide cogent new evidence on the mechanisms that connect bacterial lyophilates to abnormal responses to pathogenic airway viruses and bacteria, and the development of asthma exacerbations. Navarro et al[111] showed in sensitized mice that oral administration of Broncho-Vaxom suppressed eosinophilic airway inflammation and bronchial hyperresponsiveness through IL-10− and MyD88-dependent mechanisms and induced the conversion of FoxP3(−) T cells into FoxP3(+) Treg cells. In addition, CD4(+) T cells purified from the trachea of Broncho-Vaxom–treated mice conferred protection against eosinophilic airway inflammation when adoptively transferred into sensitized mice. Strickland et al[112] showed that oral Broncho-Vaxom markedly boosts baseline levels of $CD4^+CD25^+Foxp3^+$ Treg cells in airway mucosal tissues in rats, and that animals with boosted mucosal Treg-cell defenses show strong attenuation of both eosinophilic airway inflammation and bronchial hyperresponsiveness. Taken together, these results suggest that Broncho-Vaxom induces the expansion of Treg cells in the gut, which in turn migrate to the lung mucosa and protect against excessive airway inflammation.

In summary, these data support the hypothesis that Broncho-Vaxom could decrease the frequency of exacerbations in subjects with eosinophilic asthma.

Pharmacology.—The study intervention will be Broncho-Vaxom, 7-mg capsule, containing lyophilized bacterial lysates, as described earlier. The dose will be one 7-mg capsule per day on an empty stomach for 4 months. There is no known drug interaction for Broncho-Vaxom. No clinical data on exposed pregnancies are available. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/fetal development, parturition, or postnatal development. No specific studies have been

performed, and no data have been reported for breast-feeding women and their children. Given the composite nature of the product, the active components within the lyophilisate that explain its putative therapeutic effects are unknown.

Potential predictive and monitoring biomarkers.—Blood eosinophils will be used as predictive biomarker, specifically blood eosinophils more than 300/μL. There is no human data suggesting that effects of Broncho-Vaxom in patients with asthma occur preferentially in a specific subgroup of patients. However, in animal models of airway inflammation, Broncho-Vaxom is associated with a marked downregulation of airway eosinophilia.[111,112] Although the ideal predictive biomarker would thus be sputum eosinophils, reliably ascertaining this phenotype is difficult, and often requires more than 1 sputum induction. Therefore, blood eosinophils were chosen as predictive biomarker, and sputum eosinophils will be used as an exploratory predictive biomarker. We will use 150 eos/mm^3 of blood as the cutoff point for blood eosinophilia.

The main intervention-specific response/pharmacodynamic biomarker will be the composition of the stool microbiota. Our hypothesis is that Broncho-Vaxom may exert its effects either by direct Treg-cell induction, as suggested by experimental studies,[111] or by creating the conditions within the mucosal-microbiome interface for the growth of bacteria that in turn induce such cells. This hypothesis is supported by studies showing that administration of *Lactobacillus reuteri* to mice increased the activation of nonantigen-specific CD4(+)CD25(+)Foxp3(+) Treg cells, which in turn attenuated allergic airway responses.[113]

Safety monitoring considerations.—Broncho-Vaxom is an investigational preparation in the United States; however, it has a compelling safety record over many years of study and clinical use in the European Union and other regions. The safety profile of Broncho-Vaxom has been established by a longstanding and large experience, which includes several adequate placebo-controlled clinical trials as well as extensive postmarketing data. In the 9 double-blind, placebo-controlled, randomized core efficacy and safety trials in the approved indications, 1071 patients have been exposed to Broncho-Vaxom, including 552 adults (7-mg dose) and 519 children (3.5-mg dose). Safety information is also available from 8 double-blind, placebo-controlled, randomized clinical trials of Broncho-Vaxom in additional adult and pediatric populations, including 704 adults (7-mg dose) and 430 children (3.5-mg dose), of whom 43 were aged 6 to 18 months, and from 1 controlled randomized special safety study in the literature. The global incidence of adverse effects revealed in these clinical studies is between 3% and 4%. Importantly, currently the worldwide postmarketing safety experience is estimated at more than 44 million adult and 43 million pediatric patients treated with Broncho-Vaxom.

In a recent meta-analysis of clinical trials of Broncho-Vaxom for chronic obstructive pulmonary disease, Pan et al[110] reported a 1.75-fold increase in “abdominal problems” (CI, 1.05–2.88; total N = 471). The most frequently reported abdominal problem is diarrhea, which appears to be easily reversible after discontinuation of the product. In participants who present with diarrhea, vomiting, or abdominal pain while on Broncho-Vaxom or placebo, treatment will be interrupted until 2 days after resolution of symptoms,

at which time treatment will be restarted. If symptoms relapse, the participant will be withdrawn from the Broncho-Vaxom trial. No other specific safety monitoring will be established. To ensure participants safety, subjects with the following conditions will be excluded from treatment with Broncho-Vaxom: (1) known hypersensitivity to lyophilized bacterial products; (2) history of inflammatory bowel disease, rheumatoid diseases, or other autoimmune diseases that are currently or within 3 months of screening being treated with immunosuppressive/immunomodulatory agents (including methotrexate, prednisone, mycophenolate, sulfasalazine or azathioprine cyclophosphamide, a cytotoxic agent, cyclosporine, tacrolimus, oral or parenteral gold, or penicillamine); and (3) a history of bowel-shortening or gastric bypass surgery.

Cavosonstat (GSNOR inhibitor) (Working Group Chair: Dr Ben Gaston, Indiana University)

Rationale.—S-Nitrosoglutathione (GSNO) is an endogenous bronchodilator in the human airways. Concentrations in the normal human airway are close to the IC_{50} for relaxing human airway smooth muscle. In the case of human airway smooth muscle, the relaxation is cyclic guanosine monophosphate (cGMP)-independent.[114,115] In asthmatic respiratory failure, however, GSNO levels are paradoxically low, despite high levels of NO radical in the exhaled air.[116,117] This is in part because of accelerated GSNO catabolism by GSNOR, an enzyme that reduces GSNO (using nicotinamide adenine dinucleotide plus hydrogen [NADH]) to ammonia[118,119] (Fig 7). Indeed, knocking out murine GSNOR protects against experimental asthma.[120] Furthermore, GSNOR is upregulated by IL-13[121] and causes inflammation.[121,122] GSNOR is also required to permit tachyphylaxis to β agonists through loss of the cell surface expression of the β2 receptor.[123,124]

Consistent with these data, GSNOR single nucleotide polymorphisms (SNPs) are associated with asthma risk and impaired β2 response,[123,125,126] and 2 articles suggest that there is a gene-gene interaction such that decreased β2 function and increased GSNOR activity predict both asthma and asthmatic intensive care unit admission.[125,126] Of note, these same SNPs were identified in the SARP population to be associated with impaired β2 response (Fig 7). Direct bronchoscopic analysis confirms that airway mRNA for gsnor (*adh5*) is higher in patients with wild-type SNPs (those associated with decreased β2 response) than in the patients with variants associated with good β2 response. Bronchoscopic biomarker assays reveal that, in humans, airway GSNOR activity is increased in approximately 40% of patients with asthma in general, and severe asthma in particular.[121,127,128] On the whole, patients in SARP with increased GSNOR activity in their airways tended to be younger, thinner, and more atopic,[121] but were not characterized as having high type 2 inflammation based on eosinophil counts.

GSNOR inhibition by Cavosonstat is safe and well tolerated. It decreases sweat chloride modestly in cystic fibrosis.[129] However, Cavosonstat is not therapeutically ideal for treating cystic fibrosis because there is very little substrate made in the airways of patients with cystic fibrosis (without exogenous nitrite or NO).[117] Because GSNO is made and turns over rapidly in the airways of some people with asthma,[121,128,130,131] Cavosonstat may be better suited for the subpopulation of patients with severe asthma with increased airway GSNOR activity.

Pharmacology.—The dose of Cavosonstat will be 50 mg by mouth twice daily. The molecule is a potent GSNOR inhibitor, and the dose is selected to achieve optimal inhibition. The half-life is approximately 10.5 hours. Oral Cavosonstat (N91115) is blended with commonly used excipients and formulated in size 1, off-white capsules with a total fill weight of 300 mg per capsule. We do not anticipate interactions with controller medications, based on drug-drug interaction studies done to date in humans. Furthermore, there were no drug-drug interactions with asthma medications taken by patients with cystic fibrosis in the phase 2 trials.

Predictive and monitoring biomarkers.—The best biomarkers for predicting response to GSNOR inhibition would be airway GSNOR activity assays. These are done by bronchoscopy[117,120,121] or breath condensate.[128] Because neither procedure is anticipated in the PrecISE Network for screening all subjects, we will instead perform genotyping for GSNOR/adh5 SNPs associated with asthma[123,125,126] and with β2-agonist responsiveness.[125,126] To validate this approach, we have queried asthma phenotypes in the SARP population. The 2 principal SNPs reported by Choudhry et al[125] were independently identified to be associated with impaired β2-agonist responsiveness in SARP, such that the combination of 2 SNPs in the 3′ untranslated region (rs 7669660 TTand rs 11547772 AA) was associated with 3% less response than the rs 7669660 CC or CT and rs 11547772 CA or CC combinations and increased adh5 mRNA in airway biopsies from human subjects with asthma. Therefore, the predictive biomarker for PrecISE is genotype rs7669660 TT and rs11547772 AA, with predicted allele frequencies of at about 64% (Gaston B, unpublished data, 2021). However, when the data were reanalyzed for response to only 4 puffs of albuterol, it was only the Black population that was significantly less responsive in the presence of the high GNSOR expression SNPs. Therefore, we believe that we will have the best chance of identifying a biomarker-based response in the target population if we obtain pretreatment and posttreatment maximum bronchodilation data for those subjects selected for the Cavosonstat arm. Note that improved β response is only being used as a biomarker here, not as a primary outcome. It could be argued that improved β2 response may not always be desirable in severe asthma, particularly if there is a proinflammatory component to β2 signaling, as argued by Bond and others. Independent of the effect on the β2 adrenergic receptor, GSNO intrinsically relaxes human airway smooth muscle, overcomes cholinergic bronchoconstriction, and decreases airway inflammation.[114–116,118–122]

Safety and monitoring considerations.—Phase 1 studies showed no human AEs that differed in frequency from placebo.[129] This is consistent with the preclinical toxicology data. High doses in murine models led to increases in alanine aminotransferase and aspartate transaminase values that were accompanied by minimal to mild single hepatic cell necrosis and/or minimal focal necrosis in the liver. Partial to full recovery of these findings was observed at the end of the 28-day recovery period.

Itacitinib (Janus kinase inhibitor) (Working Group Chair: Dr Michael Wechsler, National Jewish Health)

Rationale for selection.—Itacitinib adipate (INCB039110 adipate, developed by Incyte) is a novel, potent, and selective Janus kinase (JAK) inhibitor with selectivity for JAK1.

JAK proteins are intracellular kinases that play a critical role in signal transduction through numerous cytokine and hormone receptors. JAK signaling results in activation of signal transducer and activator of transcription (STAT) proteins, which are intracellular transcription factors. STATs in turn directly bind DNA and regulate gene expression. The JAK-STAT pathway is now recognized as a critical signaling cascade involved in immune and inflammatory reactions.[132] Type 2 asthma cytokines IL-4 and IL-13 activate STAT6 in their target cells (eg, airway epithelial cells), and experiments using gene-targeted knockout mice confirmed a key role for STAT6 in type 2 responses, IgE production, bronchial hyperresponsiveness, airway remodeling, and mucus metaplasia after allergen sensitization.[133] STAT6 expression is elevated in patients with asthma in the lower airways of some but not all patients.[134] Other asthma-associated cytokines also signal through JAK/STAT proteins including IL-5 and thymic stromal lymphopoietin.[135] Because these key type 2 asthma cytokines (IL-4, IL-5, IL-13, and thymic stromal lymphopoietin) act through JAK signaling, there is a potential role for JAK inhibition for the treatment of type 2 asthma. Experiments in mouse models also support the idea that inhibiting JAK1/3 will attenuate allergen-induced lung inflammation.[136,137]

Because aberrant production of cytokines and growth factors has been associated with asthma and JAK1 has been shown to cooperate with other JAKs to mediate the signaling of a number of inflammatory cytokines, most notably type 2 cytokines including IL-4, IL-13, and thymic stromal lymphopoietin, as well as IL-6, we hypothesize that the orally available JAK inhibitor itacitnib can serve as a novel precision-based targeted approach for severe type 2 asthma. Because non–type 2 asthma also likely involves JAK-dependent cytokine receptor signaling (eg, via IL-6 and IFN-γ), there may also be a broader role for JAK inhibition in both type 2 and non–type 2 asthma.

Pharmacology.—The dose of itacitinib administered will be 200 mg (2 × 100 mg tablets) taken once daily by mouth. This is the current dose being studied in a phase 3 study in graft-versus-host disease (protocol no. NCT03139604). Itacitinib dose selection for that study was based on efficacy and safety of itacitinib from other dose-ranging studies. The higher incidence of thrombocytopenia in a 300-mg cohort, as well as similarities in pharmacokinetics and efficacy between dose groups, led to the identification of the 200-mg dose of itacitinib as the recommended dose for subsequent clinical trials.

Potential predictive and monitoring biomarkers.—Type 2 cytokines including IL-4, IL-5, and IL-13 all work through JAK-dependent mechanisms. Because IL-4 and IL-13 are major inducers of nitric oxide synthase in airway epithelial cells and signal through STAT6, we speculate that FENO measurements will provide a good marker of target engagement. FENO predicts response to IL-4 receptor alpha antibodies, with a cutoff point for response of approximately 20 ppb. FENO has been shown to decrease with anti–IL-4 receptor therapy. Furthermore, a recent clinical study demonstrated proof of concept that an inhaled JAK1 inhibitor reduces FENO in ICS-naive patients with mild asthma.[138] This validates the idea of using FENO as a marker of target engagement for JAK1 inhibition. High blood eosinophils (≥300) also identify responders to IL-4/13 therapies, likely through effects on eosinophilic trafficking and various chemokines (eotaxins) and/or IL-5. In addition, IL-5

signaling involves JAK pathways; therefore, blood eosinophil counts should also decrease on JAK inhibitor therapy. We propose to use both FENO and blood eosinophil counts as predictive biomarkers to identify patients with type 2 asthma who will respond to JAK inhibitors. Specifically, we will target patients with either FENO more than 20 ppb or eosinophil count greater than or equal to 300/μL. From the SARP data set, we estimate that 51% of patients enrolled will have FENO more than 20 ppb and that 41% of patients enrolled will have blood eosinophils greater than or equal to 300. Collectively, 64% will have 1 or the other criteria. We also propose to measure CRP using the high-sensitivity CRP test as a response/pharmacodynamic biomarker.

Safety monitoring considerations.—In the ongoing and completed clinical pharmacology studies, itacitinib was generally safe and well tolerated in healthy subjects, with few discontinuations. In clinical trials of subjects with other conditions (eg, graft-vs-host disease or psoriasis), treatment-related side effects included transient neutropenia, decreased reticulocyte count, minor dose-related decreases in platelet count, and dose-independent increases in mean lipid values and serum iron.[139,140] Most treatment-emergent AEs were mild in severity. There have been no clinically significant, unanticipated safety findings or trends observed. However, based on preclinical and clinical experience with itacitinib, as well as other JAK inhibitors,[141] the major potential risks with itacitinib include (1) serious infection and opportunistic infections, (2) viral reactivation, (3) malignancy and lymphoproliferative disorders, (4) decreased lymphocyte counts, (5) decreased neutrophil counts, and (6) alterations in the lipid profile.

Because of the potential risk of infections with the administration of JAK inhibitors including itacitinib, subjects with acute and chronic infections, history of recurrent infections, and/or latent infections will be excluded from the studies with this compound. Subjects will be closely monitored for the development of signs and symptoms of infection during the studies. A patient who develops a new infection during treatment with itacitinib will undergo a prompt and complete diagnostic testing appropriate for an immunocompromised patient, appropriate antimicrobial therapy will be initiated, and the patient will be closely monitored. Itacitinib will be discontinued in subjects with serious infections requiring hospitalization, parenteral antimicrobial therapy, or as otherwise judged clinically significant by the investigator.

Anticipated outcomes.—The 3 primary outcomes for each intervention in PrecISE are prebronchodilator FEV_1, ACQ-6 score, and a surrogate for asthma exacerbations (CompEx[109]). An intervention will be considered successful if it meets end points for any 1 of the 3 primary outcomes. More information about our plans for outcome assessment, subgroup refinement, and statistical analysis are available in our recent publications.[9,10] In the following section, we review how these outcomes and other procedures in the network will be measured.

5. PROCEDURES IN THE PrecISE NETWORK PROTOCOL

The PrecISE study has incorporated several novel procedures to facilitate the execution of the Master Protocol and the scientific goals of the network. Procedures that subjects undergo

as they progress through screening, into run-in, and through randomization to the end of the protocol will be considered here. This includes the procedures necessary for screening of subjects, developing the necessary predictive biomarker profiles for treatment assignment, and performing other key phenotyping of enrolled subjects in the PrecISE Network. The mechanics of the collection of data necessary to detect CompEx events, 1 of the 3 primary end points of the study, will also be discussed. CompEx is unique among the end points in that it requires twice-daily capture from subjects to calculate events.

Screening

Prebronchodilator spirometry will be done at screening after withholding baseline asthma medication for specified periods of time up to 36 hours, depending on the agent. Postbronchodilator spirometry will be performed at screening as a maximum bronchodilator maneuver with up to 8 puffs of albuterol. These measurements may be used to meet inclusion criteria establishing evidence of asthma and establishing the presence of baseline poor or uncontrolled disease. At subsequent visits during the protocol, bronchodilator challenge is performed using 4 puffs of albuterol. Methacholine challenge spirometry may also be performed during the screening process to demonstrate evidence of asthma if bronchodilator responsiveness does not meet the thresholds of 12% and 200- mL increase in FEV_1.

The ACQ-6 is administered at screening as part of the determination of baseline asthma control.[142,143] An ACQ-6 score of 1.5 or more is considered as poor control.[144] Subjects are also given validated questionnaires at screening that will facilitate characterizations of common comorbidities that may influence asthma. These include the following:

- Sleep apnea: STOP-BANG
- Gastroesophageal reflux disease (GERD Questionnaire)
- Vocal cord dysfunction (Pittsburgh Vocal Cord Dysfunction Index)
- Chronic rhinitis sinusitis (Sinonasal Questionnaire)
- Depression-Anxiety (Hospital Anxiety and Depression Scale)

Participants who meet the established cutoffs for these questionnaires are evaluated by the investigator to consider the clinical significance of the positive questionnaire based on history, physical, and available testing. The investigator will need to judge the presence, severity, and control of a specific condition and determine whether it is sufficiently controlled to keep the participant in the PrecISE protocol. If the comorbid condition(s) is not adequately controlled, the investigator may refer the participant for further evaluation/ treatment, before enrollment in PrecISE.

Biomarkers (Committee Chair, Dr Wanda O'Neal, University of North Carolina)

As detailed elsewhere in this report, and in a previous publication from the PrecISE Network,[9] the measurement of predictive biomarkers is integral to the study design. Based on biomarker profiles, a determination will be made as to which participants should be targeted by which interventions. The biomarker profile determined at screening will be used

to inform the randomizations at all treatment periods. Sample collection will also allow for assessment of an array of exploratory biomarkers that may predict and/or have utility in monitoring treatment response.

To obtain information needed for randomization, the following biomarkers will be obtained during the run-in period:

- **a.** Blood eosinophils: The absolute eosinophil count is part of the primary predictive biomarker profile for planned PrecISE interventions imatinib, itacitinib, and bacterial extract (Broncho-Vaxom). The predictive biomarker threshold for imatinib is an eosinophil count of less than 300 cells/μL, whereas for itacitinib and bacterial extract the threshold is greater than or equal to 300 cells/μL.
- **b.** SNP genotypes associated with increased GSNOR activity: These polymorphisms serve as the primary predictive biomarker for Cavosonstat.
- **c.** Plasma IL-6: The predictive biomarker threshold for clazakizumab is a plasma IL-6 level of greater than or equal to 3.1 pg/mL.
- **d.** FENO: FENO level of more than 25 ppb is part of the primary predictive biomarker profile for itacitinib. FENO level of greater than or equal to 15 ppb is the predictive biomarker for the MCT intervention.

A series of secondary and exploratory predictive biomarkers for each intervention planned in PrecISE is obtained from blood, urine, sputum, and CT scan of the chest.[9] CT scanning and sputum collection methodology are described in further detail below. In addition to the predictive biomarkers obtained in the run-in period, monitoring biomarkers for each intervention are obtained at regular intervals through the treatment periods (see “Study Medications” section).

CT scanning (Committee Chair, Dr Mario Castro, University of Kansas)

The PrecISE Master Protocol provides a unique opportunity to incorporate lung imaging techniques to develop novel exploratory, imaging-based biomarkers that may predict response to interventions. Imaging is a noninvasive means of monitoring airway structure and remodeling (eg, thickened airway walls), air trapping, mucus plugs, and other parameters of peripheral airway pathologies. Furthermore, imaging may help identify individuals with asthma who are likely to develop severe disease and who may benefit from early targeted, aggressive therapy.

High-resolution CT scan of the chest will occur at the qualification visit following 4 puffs of albuterol in subjects who meet entry criteria. The PrecISE Radiology Center (University of Iowa, Dr Eric Hoffman) provides standardization and harmonization of all CT imaging protocols performed in PrecISE. In addition, the center provides initial quantitative CT analysis of all images. The basic CT scanning protocol for PrecISE participants consists of obtaining multidetector CT images of the entire lung at coached full inspiration (total lung capacity [TLC]) and at a coached full expiration (residual volume [RV]). TLC and RV scans will be performed at visit 0 (run-in visit) in all participants who have consented to

CT. Adolescents (age 12–17 years) will receive CT scans only at those sites that are able to perform low-dose imaging (low dose is defined as a total exposure of ~3–5 mSv in an average-weight individual). Scans will be read by local radiologists to rule on the presence of clinically actionable conditions, such as pneumonia or nodules.

Unique breathing instructions are required to obtain appropriate images.[145] PrecISE sites are required to use the newest/most modern CT scanner available at their sites to use newer technology of dose modulation and iterative reconstruction. (If a site does not have a new-enough scanner, for adult subjects only, they will use a fixed protocol based on the body mass index of the subject.) By using dose modulation, we are able to to get the same-quality image and signal-to-noise ratio for differing body types. With the addition of iterative reconstruction, we can use a low-dose protocol and reduce the noise in the images while keeping the accuracy of the data.

CT scans will be analyzed using automated, quantitative airway evaluation software designed to reconstruct 3-dimensional lungs, lobes, and airway trees from multidetector computerized tomography images (VIDA|vision, VIDA Diagnostics, Australia). Analysis will provide airway and parenchymal-based metrics. Using existing techniques, the lungs will be segmented to identify left and right lungs along with their associated lobes. Total volume, as well as air and tissue volumes, will be reported for the whole lung, right and left lungs, and for each individual lobe. Local statistical measures of lung parenchymal attenuation values will be computed for each lobe and sublobar region. Parenchymal measures from the TLC scans will include percentage of total volume below (or equal to) −950 and −910 density histogram-based mean, SD, skewness, and kurtosis for the whole lung, left and right lungs, and lobes. Air trapping on the RV scans will be defined as the percentage of voxels (on a whole lung, left and right lungs, and lobar basis) falling below (or equal to) −856HU. The TLC and RV scans will then be registered and processed by VIDA's Disease Probability Measure to generate regional probability maps[146,147] of what has been termed functional small-airways disease, normal parenchyma, and emphysema-like (or hyperinflation). These measures will be provided for the whole lung, left and right lungs, and lobes. The image matching of TLC to RV also provides regional maps of Jacobians (local volume change) and Jacobian SDs, and regional Anisotropic Deformation Indices along with the Anisotropic Deformation Indices SDs.[148]

The airway tree will be segmented to include 5 primary paths (passing through RB1, RB4, RB10, LB1, and LB10). The VIDA|vision software automatically labels airway segments, which are subsequently reviewed by VIDA-certified analysts and placed according to standard bronchoscopic terminology. Airway segmentation at TLC is expected to yield up to 7 to 9 generations of the airway tree. Maximum and minimum diameters will be reported for the middle third of each segment (avoiding the branch point saddles); segment lengths will be included, which permit the calculation of segment luminal volumes. Airway wall thickness will be reported for the middle third of each segment. Airway wall thickness will be normalized to the lumen plus wall area to provide a wall area percent measure for each found segment, and a Pi10 measure will be reported for each of the above-named 5 paths. This measure is derived from a plot of the inner perimeter (x-axis) versus square root of the airway wall area (x-axis), identifying a regression line and identifying the modeled airway

wall area associated with a hypothetical inner perimeter of 10 mm using the relationship defined by the regression.

Induced sputum collection (Committee Chair, Dr John Fahy, University of California San Francisco)

Induced sputum will be collected from PrecISE participants at the run-in visit. Sputum induction is a relatively simple, repeatable, and noninvasive method to collect airway secretions. Thus, sputum is a highly asthma-relevant biological sample type. Sputum samples will provide an opportunity to establish the inflammatory cell differential and counts in the patient's airways, while providing an opportunity for extended studies (eg, gene expression, microbiome, and sputum biomarkers such as tryptase). Cellular and biochemical analyses of induced sputum samples collected from participants with and without asthma have revealed differences in markers of eosinophilic inflammation and bronchovascular permeability in a population with asthma.[149] Similarly, sputum-induced samples have revealed the expected rise (following an antigen challenge) and fall (following a prednisone treatment) of markers of eosinophilic inflammation.[150,151]

Sputum cell counts in PrecISE are determined in a central core laboratory. Other sputum biospecimens are stored in the PrecISE Biorepository after processing. The process of sputum collection involves nebulization of 3% saline to induce cough and sputum production. Hypertonic aerosols such as 3% can induce bronchoconstriction in patients with asthma, and pretreatment with albuterol will be provided to guard against such bronchoconstriction. In addition, participants with low FEV_1 will undergo sputum induction with an isotonic aerosol (0.9% saline). Specific and standardized procedures for sputum induction have been established for the PrecISE Study. The procedures for sputum induction differ in adults and in adolescents, as follows, with differences designed to have a more conservative protocol in the adolescents:

- *Adolescents:* For participants with a postbronchodilator FEV_1% greater than or equal to 70%, sputum is induced using 3% saline; for participants with a postbronchodilator FEV_1% less than 70%, sputum is induced using 0.9% saline.
- *Adults:* For participants with a postbronchodilator FEV_1% greater than or equal to 50%, sputum is induced using 3% saline; for participants with a postbronchodilator FEV_1% less than 50%, sputum is induced using 0.9% saline.

CompEx-related procedures (Committee Chair, Dr Praveen Akuthota, University of California San Diego)

The use of CompEx events as a primary end point provides an outcome with statistical properties that approximate exacerbations but with a shorter follow-up time.[109] CompEx is a composite outcome specific to asthma that combines clinically relevant deteriorations captured by diary events with exacerbations, thereby providing an increase in power compared with using exacerbations alone. Critically, use of the CompEx rather than exacerbations alone allows for the PrecISE Master Protocol to incorporate 16-week treatment periods, facilitating the study of multiple agents. The use of exacerbations as a primary end point in asthma clinical trials has traditionally required much longer treatment

periods, often 52 weeks, which would be wholly impractical from an implementation perspective for a master protocol designed as a platform for multiple interventions. Statistical considerations for the use of CompEx in PrecISE were discussed in a previous publication.[10] Exacerbations alone will be analyzed as a secondary efficacy end point.

In addition to exacerbations, CompEx events include deterioration events defined on the basis of (1) daily recordings of peak expiratory flow morning/evening (L/min); (2) inhaled reliever medication use (ie, short-acting β-agonist) morning/evening (doses); and (3) symptoms morning/evening (score 0–3) assessed from twice-daily diary recordings. Because CompEx event detection relies on twice-daily peak flows, reliever use counts, and symptom scores in a study with a planned enrollment period of up to 30 months, it was critical for the PrecISE Study to incorporate methodology and tools to facilitate real-time capture of the necessary data streams. To this end, the PrecISE Network has partnered with Propeller Health, maker of an inhaler sensor-driven asthma management platform, and have adapted the Propeller platform to capture the CompEx variables in a clinical trial environment.

At the time of enrollment, the Propeller Health application is installed on the subject's smart phone (either iOS or Android). The application prompts subjects to answer twice daily diary questions that will allow for the collection of the requisite symptoms scores for CompEx. Participants will be asked to describe their morning symptoms using the following scale: 0, No symptoms to report; 1, I was aware of my symptoms but they were easily tolerated; 2, I had problems sleeping due to my asthma; 3, I could not sleep because of my asthma. Participants are asked to describe their evening symptoms using the same scale.

Peak flows are measured twice per day using a spirometer (Spirobank Smart; Medical International Research, Rome, Italy) that connects to the subject's smart phone via Bluetooth wireless through the Propeller application. Subjects are asked to complete 3 peak flow maneuvers each morning and 3 peak flow maneuvers each evening.

Reliever inhaler usage is monitored using sensors that fit over the metered-dose inhaler and connect to the participant's phone by Bluetooth via the Propeller application. The reliever metered-dose inhaler sensor records the date and time of inhalations in the sensor, allowing for doses of reliever in the morning and in the evening to be used for the calculation of CompEx events.

Symptom diaries, peak flows, and rescue usage data collected by the Propeller system is transferred to the PrecISE DMCC at regular intervals. In the case of technical barriers preventing electronic data collection from individual subjects, the study has incorporated a system of paper data collection fail safes. The CompEx tool was developed by a pharmaceutical company (AstraZeneca), and the PrecISE Network has partnered with them to obtain the source code for calculation of CompEx events and for technical assistance in implementing the algorithm.

A CompEx event can occur as defined by threshold and slope criteria within a moving window of 5-day length. Evening and morning recordings are treated as separate variables. The thresholds for each variable are based on a baseline that is calculated for each individual as the mean over the 5 to 10 days ending just before the day of randomization for each of

the diary variables. No imputation of missing diary data after randomization is performed. Deterioration criteria are assessed for each (single) diary variable for thresholds and slopes as follows:

- *Thresholds*: The change from baseline is calculated. If 2 consecutive days fulfill the chosen threshold limit as defined in Table III, the deterioration criterion is met.
- *Slopes:* A slope is calculated via linear regression over 5 days. If the slope fulfills the chosen cutoff point as defined in Table III, the deterioration criterion is met.

A CompEx event can occur when (1) the threshold deterioration criterion is met for at least 2 variables, or when (2) the threshold deterioration criterion is met for 1 variable, and the slope criterion is fulfilled for all included variables. In case of (1), the event is defined to start on the first day of the 2 consecutive deterioration days. In case of (2), the event is defined to start on the first of the 2 days fulfilling the threshold criterion. (This means that the slopes are calculated for days −4 to 0 of an event.) To be counted as a new diary event, it must be preceded by at least 7 days in which neither criterion for a diary event is fulfilled.

Adherence monitoring

The PrecISE study will also use the Propeller Health platform to monitor adherence to background controller medications using Bluetooth-connected sensors that are compatible with several commonly used delivery devices for ICSs, long-acting β-agonists, and combination inhalers. To qualify for randomization, subjects who pass initial screening must demonstrate 70% adherence to background controller medications during the run-in period as measured by electronic monitoring (or back-up paper reporting if needed). The PrecISE Network has partnered with a pharmaceutical company (GlaxoSmithKline) to provide background controller inhaled medication compatible with the Propeller platform (fluticasone/salmeterol in Diskus formulation). However, subjects can choose to stay on their previous controller medications if they wish. Adherence will be continued to be monitored after randomization using the Propeller platform.

Biobanking (Biorepository Lead, Dr Suzy Comhair, Cleveland Clinic)

The PrecISE Study has incorporated a comprehensive biobanking strategy that will allow for development of ancillary research studies leveraging the network’s unique cohort of patients with severe asthma. Plasma, serum, sputum, and urine are all collected during the run-in period and stored at the PrecISE Central Biorepository. PAXgene RNA tubes (BD Biosciences, Franklin Lakes, NJ) are collected, facilitating future research on bulk blood RNA. Recognizing the need to be able to do more detailed immunophenotyping, PrecISE sites will also be purifying PBMCs from blood, followed by cryopreservation and storage at the biorepository.

6. PROTOCOL IMPLEMENTATION AND ADAPTATIONS FOR COVID (PROTOCOL IMPLEMENTATION COMMITTEE CHAIR DR LOREN DENLINGER, UNIVERSITY OF WISCONSIN)

The PrecISE Network screened the first participant on December 31, 2019. With the emergence of the COVID-19 pandemic, the network placed a hold on screening new participants on March 9, 2020, and halted all PrecISE Study visits on March 16, 2020. At that time, 13 participants were in the run-in phase and none had been randomized. Regular phone contact and provision of study albuterol and fluticasone-salmeterol by mail facilitated continued engagement of 11 of these participants until study visits resumed in June 2020. Acknowledging variation in local institutional guidelines, sites were allowed to reopen when safety clearance had been documented supporting the ability to perform spirometry, phlebotomy, and FENO measurements at in-person study visits as the minimally necessary study procedures to assess inclusion criteria, key phenotypic biomarkers, and baseline primary outcome measures.

While the PrecISE trial was on hold, the FDA issued updated guidelines (Docket FDA-2020-D-1106) for clinical trial conduct during the pandemic on May 14, 2020, and additional considerations for trial integrity were outlined by Fleming et al.[152] These documents contained several recommendations for trial launch logistics, maximizing adherence to study interventions, maintenance of uniform data collection methods, and adjustments to analytic plans. Because of concerns about the impact of subsequent waves of the pandemic on the trial, the Protocol Implementation and Design Committees developed a plan to identify study activity adaptations and to inform the PrecISE SC and DSMB by the July 21, 2020, meeting. The primary objectives for these adaptations were to ensure safety of participants and study staff while maintaining the scientific integrity of the study. An outline of this plan is presented in the remainder of this section.

The adaptive design of the PrecISE trial integrates both predictive and monitoring biomarkers, creating a potential tension between maximizing safety and preserving innovation.[10] Many of the advanced phenotyping measures in the protocol require in-person study visits, such that complete conversion to remote study activities and data collection for the entire duration of the trial was not feasible.[9] Therefore, as a network we decided to continue with in-person phenotyping supported by previsit COVID-19 testing in accordance with local institutional safety guidelines. However, several contingency plans were enacted to weather subsequent pandemic-related site shut downs, which were anticipated to occur regionally and to occur at different times throughout the duration of the network.

Given the variable local/institutional restrictions for in-person study visit conduct, compounded by likely ongoing participant concerns about coming to PrecISE centers for study visits, we have developed approaches to allow for performing the informed consent process remotely. In this case, the consent form will be provided to the participant by email or mail, and then reviewed with the participant over the phone or during a video call. The participant may sign the consent form and return it to the site, or the form may be

signed electronically, provided a software tool that is compliant with the Code of Federal Regulations 21 Part 11 concerning electronic signatures is available at the site.

Protecting the primary end points is also paramount. For the PrecISE trial, the primary end points are FEV_1, the ACQ-6 score, and the CompEx measure of loss of asthma control events.[109,153] Fortunately, the ACQ-6 has been adapted for use at home,[154] and we had already contracted with Propeller Health to collect the eDiary, peak flow, and rescue albuterol use data needed to calculate the CompEx scores. The peak flow meter for the trial is the Spirobank Smart device, which is also capable of generating spirograms and flow-volume loops. The protocol was also adapted to allow for home spirometry measurements to provide baseline and interim lung function measurements. Home spirometry uses the ZEPHYRx software (Troy, NY), which captures flow-volume loops and allows virtual, real-time coaching by the study coordinator. At the time of this writing, in an effort to achieve remote collection of FEV_1 measurements, we have launched a pilot program to test the feasibility of coordinator coaching of participants through video conference tools with workflows to enable central overreading of these spirometry sessions. During the pilot, FEV_1 will be measured remotely (at home) and at in-person visits, with the plan to present comparative analyses to the DSMB by early 2021.

Finally, we designed procedures to optimize safety and accessibility of study interventions. For participants already randomized at a site affected by a regional shutdown, distribution of study drug by mail is planned for oral and inhaled medications, whereas injections will continue to be delivered in person (on site), barring local institutional restrictions. We have developed a mechanism for collection of safety monitoring lab tests by a regional commercial laboratory service, avoiding the need for participants to come to PrecISE academic medical centers for phlebotomy. In addition, in context of widespread COVID-19 vaccination, we recognize the theoretical potential effect of immunomodulating interventions on vaccine efficacy and are temporarily holding randomization to those interventions to allow subjects to pursue vaccination before enrolling in the study.

7. PrecISE PPC (COMMITTEE CHAIR DR STAN SZEFLER, UNIVERSITY OF COLORADO)

It is the policy of the PrecISE SC and its PPC that all manuscripts and presentations derived from PrecISE data are submitted to the PPC to (1) conduct a scientific review, (2) ensure that there is no overlap with other planned publications, (3) set priorities and timelines for data analysis and manuscript completion, and (4) enable tracking and reporting to the SC and the NHLBI program office.

The purpose of the PPC’s scientific review is to ensure the quality and accuracy of the results presented and that the interpretation of the results is valid. In addition, the scientific review ensures that the study design and methods are accurately and consistently reported across all manuscripts and presentations.

The objectives of the PPC are to:

- Recommend policy and procedures for review and approval of all scientific communications regarding PrecISE to outside groups.
- Keep the SC informed on the status of all network presentations and manuscripts.
- Promote timely dissemination of major PrecISE findings to the scientific community.
- Encourage publications and presentations likely to have a high impact on the field and to create visibility for the work of the PrecISE Network.
- Ensure that PrecISE publications and presentations are accurate and scientifically sound, and of high quality.
- Establish a system for determining authorship on PrecISE publications and presentations that is well balanced across study investigators and sites.
- Create opportunities for investigators, especially early career investigators, from PrecISE centers and subsites to participate and be recognized in study-wide publications and presentations.
- Advise the SC on publication issues as they arise, such as with respect to industry partners.
- Approve proposals, assist in the formation of writing groups, and set priorities for all PrecISE publications and presentations, in a timely manner.
- Suggest appropriate journals for PrecISE publications to writing groups, as needed.
- Expeditiously approve publications and presentations, including those that arise from ancillary studies, before their presentation and submission for publication.
- Monitor and periodically report the status of all PrecISE manuscripts and presentations, from proposal submission to publication, to the SC, the NHLBI program office, and the DSMB.
- Manage changing priorities of presentations and manuscripts as the study progresses, taking into account allocation of resources, to ensure timely dissemination of study results.

The PPC is composed of 1 investigator from each of the 10 PrecISE CCs and a representative from the DMCC. Each member serves for a term of 2 years and is eligible for reappointment. The Chairperson of the committee is appointed by the PrecISE Executive Committee, serves for a term of 2 years, and is also eligible for reappointment. The NHLBI Project Officer and the SC Chairs sit on the PPC as ex-officio members.

Publications

All manuscripts are submitted to the PPC for tracking and reporting purposes, beginning with the manuscript proposal and continuing through journal submission and publication. Manuscript tracking and reporting are managed through an interactive manuscript tracking system.

Manuscripts are categorized as primary, secondary, or ancillary study manuscripts. Primary manuscripts focus on study design and primary results of different interventions and receive top priority in resource allocation and timelines. Secondary manuscripts focus on other scientific questions, unrelated to the primary outcomes. Ancillary manuscripts focus on research questions that are motivated by the various ancillary studies expected for PrecISE. The writing group chair is responsible for all phases of manuscript development, from conception through publication. The PPC is responsible for tracking the progress of manuscript development.

Authorship

For primary and secondary manuscripts, the lead author (writing group chair) proposes the order of authorship, subject to PPC approval. Author inclusion and author order follow International Committee of Medical Journal Editors (ICMJE) guidelines. The following options are possible authorship formats:

- **Modified Conventional:** Masthead (indexed) author = “Name A, Name B, Name C, etc for the PrecISE Research Group”; the writing group determines the order of the named authors. This is the preferred format for most manuscripts.
- **Conventional:** Masthead (indexed) author = “Name A, Name B, Name C”; the writing group determines the order of the named authors.
- **Modified Corporate:** Masthead (indexed) author = “PrecISE Research Group”; title page footnotes include a listing of the writing group for the article; the writing group determines the order of the named authors in the footnote.
- **Corporate:** Masthead (indexed) author = “PrecISE Research Group”; membership of writing group is nowhere specified in the published article.

All primary manuscripts for PrecISE use the Modified Conventional masthead. Secondary and ancillary manuscripts choose between the Modified Conventional and Conventional mastheads.

Primary manuscripts reviewed and approved by the PPC are sent to the SC for approval. The PPC reviews and authors’ responses to them are provided to the SC with the manuscript. Secondary manuscripts are also sent to the SC for approval before journal submission.

Industry review

Industry partners have the opportunity to review primary manuscripts pertaining to the use of their intervention in PrecISE, consistent with established contracts. The PPC considers any comments received from industry partners, but approval of the manuscript is not conditional on addressing those comments.

Presentations

An investigator receiving an invitation for a national or international talk on behalf of PrecISE submits an abstract of the talk to the PPC and must obtain PPC approval before submitting the abstract to the meeting organizers.

8. SAFETY MONITORING OF THE PrecISE NETWORK (COMMITTEE CHAIR, DR STEVEN WHITE, UNIVERSITY OF CHICAGO)

In a complex trial with multiple possible interventions and multiple sites, participant safety is of paramount importance. The PrecISE Network has undertaken multiple steps to ensure participant safety including the creation of a free-standing Safety Committee. Here, the Safety Committee highlights some of the measures taken to ensure patient safety during the trial.

Participants will be informed of known risks of the interventions (see Section 4) before enrollment using a common, central IRB and consent platform. Informed consent will be obtained locally at each site. As any new data become available for a particular intervention, the investigators will determine whether these would impact the study's justification or suggest a new or previously unforeseen risk that must be conveyed to the participants. The NHLBI established a DSMB to provide appropriate oversight and monitoring and to ensure the safety of participants. The study has a single IRB at Vanderbilt University. Monitoring participant safety during the study is a shared responsibility by the central single IRB, the DSMB, medical monitor, and the FDA. Locally at each site and center, the study investigator and coordinator will monitor participant safety, taking measures to ensure participant confidentiality, adhering to Health Insurance Portability and Accountability Act (HIPAA) regulations, and closely monitoring and reporting AEs.

AEs and severe AEs

Timely AE reporting is critical to enable the larger groups to monitor patient safety appropriately for the entire study. An adverse experience or AE is defined as any untoward medical occurrence associated with the use of a drug in humans whether or not it is drug related. In the PrecISE Study, such an event is considered an AE when it occurs at any point from the time of consent through 8 weeks after the last treatment (or 5 half-lives of the treatment received) (Fig 8). AEs may include a clinically important laboratory value worsening during the study or any injury, sensitivity reaction, side effect, or any other illness or condition that occurs while the participant is in the study. Preexisting disease signs, symptoms, and/or laboratory abnormalities before the use of drug are considered AEs only if they recur after the participant has recovered from the preexisting condition or if there is an exacerbation in intensity of frequency. Episodes of worsening asthma are considered an AE if the participant needs to take new medication for at least 2 days. A laboratory abnormality may be considered an AE if (1) it requires repeat testing and is confirmed when repeated, (2) the confirmed abnormality suggests a disease and/organ toxicity that is new or worsened from baseline, and (3) it requires additional active management. Active management of AEs may include reduction in study agent dose, discontinuation of the study agent, close observation, more frequent follow-up assessments, or further diagnostic investigation.

An AE is considered a serious adverse event (SAE) if either the sponsor or the investigator determine that it resulted in specific outcomes including death, life-threatening AE, inpatient hospitalization for 24 hours or more, significant incapacity, congenital anomaly, or an event that may not be immediately life-threatening but may require treatment to prevent one of the

previously listed outcomes. An AE is determined to be an SAE if it meets the definition of an SAE. All AEs are reported regardless of relationship to study medication. Timing and processor reporting AE and SAEs are outlined in Fig 8. Timely reporting of AEs and SAEs is critical to identify possible safety concerns.

Laboratory analysis

Participants have laboratory studies done as part of a safety review to (1) determine inclusion or exclusion for the study at the time of initial screening and (2) monitor for AEs during interventions. All safety lab results will be transmitted from the core laboratory (PPD, Inc) to the DMCC for review by medical monitors, after which unblinded data are forwarded to investigation sites (see Blinding and medical monitors, below). Laboratory studies done for initial safety review are listed with their guiding parameters in Table IV. For each parameter, a key consideration in study design was to determine logical, clinical thresholds. As one example, clinicians readily understand the difference between a hemoglobin value that is below the lower limit of normal (determined by a 95% CI, about 12.8 g/dL for men and 11.9 g/dL for women in most laboratories), a value that meets the definition of anemia as defined by the World Health Organization,[155] a value that raises significant clinical concern (eg, below 10 g/dL), and a “panic” value that requires immediate confirmation and treatment (eg, below 7–8 g/dL). Even for a straight-forward variable such as hemoglobin, there are age-related declines in men but not women.[156] Similarly, there are differences based on age, sex, and/or race for blood platelet and neutrophil counts,[157–159] and for estimated glomerular filtration rate.[160] Exclusion criteria, and criteria that trigger review for AEs during an intervention, were chosen with these issues in mind. We elected to deploy different threshold values for evaluation of neutropenia based on race but not for other laboratory values.

Some exclusion criteria based on laboratory values were selected to prevent participants with known immune-suppressive diseases (eg, HIV infection and tuberculosis) from receiving immune-modulating therapies. Likewise, laboratory values were selected to exclude participants with known liver disease (eg, hepatitis B, C) from receiving therapies that have a risk of inducing liver injury.

Participants will be monitored for safety during the trial, and the occurrence of certain AEs or laboratory abnormalities will result in discontinuation of the current treatment and immediate entry into a washout period. Some of the laboratory studies threshold values (including hemoglobin, absolute neutrophil count, platelet count, and alanine aminotransferase/aspartate transaminase) that mandate discontinuation differ modestly from thresholds that exclude initial participation (see Table E4 in this article’s Online Repository at www.jacionline.org); this reflects the experience of the PrecISE investigators from previous trials. Studies are monitored monthly during the treatment period. When a test meets the threshold value as reviewed by the medical monitor, a repeat test is ordered (blinded when necessary, see below) to be done by the site within 5 days. If both tests meet the discontinuation criteria, the intervention is terminated, and the participant enters an 8-week washout phase. Monitoring of the laboratory parameter in question is done at weekly intervals until the value no longer meets the threshold. Following completion of the washout

and return of the stated laboratory parameter to within an acceptable range, based on the discretion of the investigator, the participant may be randomized into a new intervention. Specific interventions may have differing thresholds for discontinuation, and both the clazakizumab and imatinib interventions have thresholds in which drug administration may proceed at a lower dose as an alternative to discontinuation as reviewed in Section 4.

Blinding and medical monitors

Participants will be monitored for laboratory abnormalities throughout the study. To ensure appropriate and timely monitoring of laboratory studies in a complex protocol, the DMCC provides a central medical monitoring system. This system consists of 2 physician scientists who serve as medical monitors and are responsible for reviewing all safety labs for participants while randomized to experimental treatments. A call system ensures that a medical monitor, or back-up, is always available. In addition to reviewing laboratory studies, medical monitors work with site investigators to resolve significant abnormalities and, when required, initiate emergency action to protect patients.

Laboratory reports will be transmitted from the core laboratory (PPD, Inc) to the DMCC daily on weekdays and will be reviewed by the medical monitors. Test results will also be made available in PPD's online Preclarus system. Sites will have access to all complete blood cell count and chemistry panel results for nontreatment visits (visit 0, visit X.1, and visit X.6) and will be responsible for reviewing and acting on these results. Because of the potential for unblinding, some laboratory studies will remain blinded to participants and study sites during treatment visits (visits X.2-X.5). Blinded laboratory studies include complete blood cell count results other than hemoglobin and hematocrit (which will remain unblinded to the sites) because neutropenia and thrombocytopenia have been reported with use of imatinib as well as clazakizumab. Only the medical monitors will have access to the blinded lab results and will be responsible for reviewing and acting on these results. The medical monitors will make decisions about the need to repeat laboratory studies, adjust the dose of study treatment, or discontinue study treatment. If the medical monitor determines that a repeat test is warranted, they will inform the site that another blood sample should be collected for analysis, but they will not inform the site of the specific abnormality. To maintain blinding of the study team, some participants receiving placebo will be randomly selected to undergo repeat laboratory draws and sham dose reductions.

In addition to the safety assessments conducted on all participants throughout the trial, some interventions will require additional safety monitoring specific to that intervention. Participants randomly assigned to an intervention or its matching placebo will receive the treatment-specific safety assessments required during the assigned periods. Performing the additional safety assessments on the matching placebo participants will help maintain the masking of treatment assignments for the study. Laboratory measurements with the potential for unmasking of study treatment will be blinded to the participant and study team and will only be available to the medical monitors and select DMCC staff. For example, imatinib use has been associated with hypophosphatemia in a proportion of patients, so serum phosphate levels will be monitored regularly in participants randomized to imatinib/placebo and phosphate supplementation initiated if needed. Some participants on imatinib placebo

will be assigned to receive phosphate placebo (see Section 4, “Itacitinib (Janus kinase inhibitor)”).

CONCLUSIONS AND FUTURE DIRECTIONS

The PrecISE Network will break new ground in clinical trials for severe and exacerbation-prone asthma. We have established the infrastructure needed to rapidly evaluate new interventions for targeted subgroups of patients with severe asthma, and identify new therapies for further development. Our clinical trial design and analytical plans outlined here and in recent publications[9,10] can serve as a reference for future studies using adaptive trial design and master protocols in this challenging group of patients. By examining the magnitude of the clinical effects observed, numbers of primary outcomes met, and size of the targeted subgroups, our industry partners can prioritize successful interventions for further clinical development in asthma. Therapies that do not meet any of the 3 primary outcomes, in contrast, should be of low priority for further development. By combining clinical outcomes with careful patient phenotyping and precision medicine analyses, the network will also advance our understanding of the pathobiology of severe and exacerbation-prone asthma.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations used

ACQ-6	6-item Asthma Control Questionnaire
AE	Adverse event
CC	Clinical center
CompEx	Composite exacerbation
COVID-19	Coronavirus disease 2019
CRP	C-reactive protein
DMCC	Data Modeling and Coordinating Center
DSMB	Data Safety Monitoring Board

EC	Executive Committee
FDA	Food and Drug Administration
FENO	Fractional exhaled nitric oxide
GSNO	S-nitrosoglutathione
GSNOR	S-nitrosoglutathione reductase
ICS	Inhaled corticosteroid
IRB	Institutional review board
JAK	Janus kinase
MC	Mast cell
MCT	Medium-chain triglyceride
NHLBI	National Heart, Lung, and Blood Institute
NO	Nitric oxide
PAC	Participant Advisory Committee
PI	Principal investigator
ppb	Parts per billion
PPC	Publications and Presentations Committee
PrecISE	Precision Interventions for Severe and/or Exacerbation-Prone Asthma
RFA	Request for applications
RTI	Respiratory tract infection
RV	Residual volume
SAE	Serious adverse event
SARP	Severe Asthma Research Program
SC	Steering Committee
SNP	Single nucleotide polymorphism
STAT	Signal transducer and activator of transcription
TCA	Tricarboxylic acid
TLC	Total lung capacity
Treg	Regulatory T

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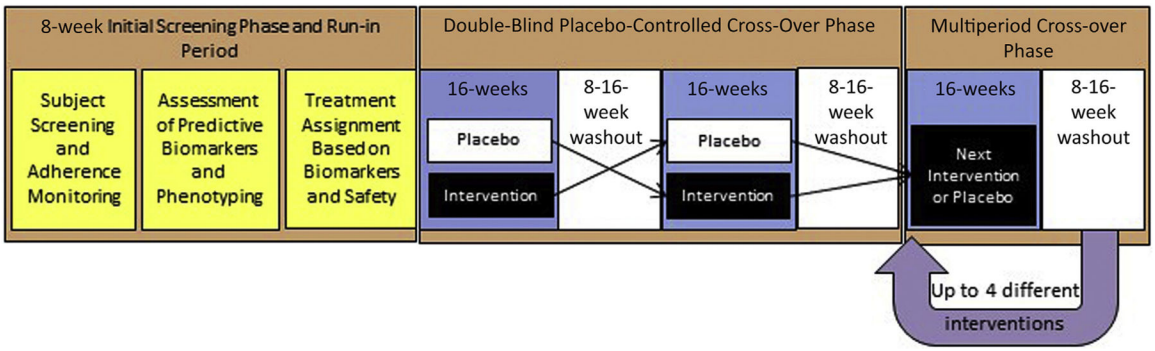

FIG 1.

PrecISE study structure. The study structure has 3 phases. First, during an 8-week initial screening phase and run-in period, subjects undergo screening and adherence monitoring, assessment of predictive biomarkers and phenotyping, followed by treatment assignment based on biomarkers and safety considerations. Second, subjects enter the double-blind, placebo-controlled cross-over phase followed by washout. The second phase varies between 48 and 64 weeks, depending on the washout duration. Finally, during the multiperiod cross-over phase, subjects can be randomized to up to 4 additional interventions. Reprinted with permission from Israel et al.9

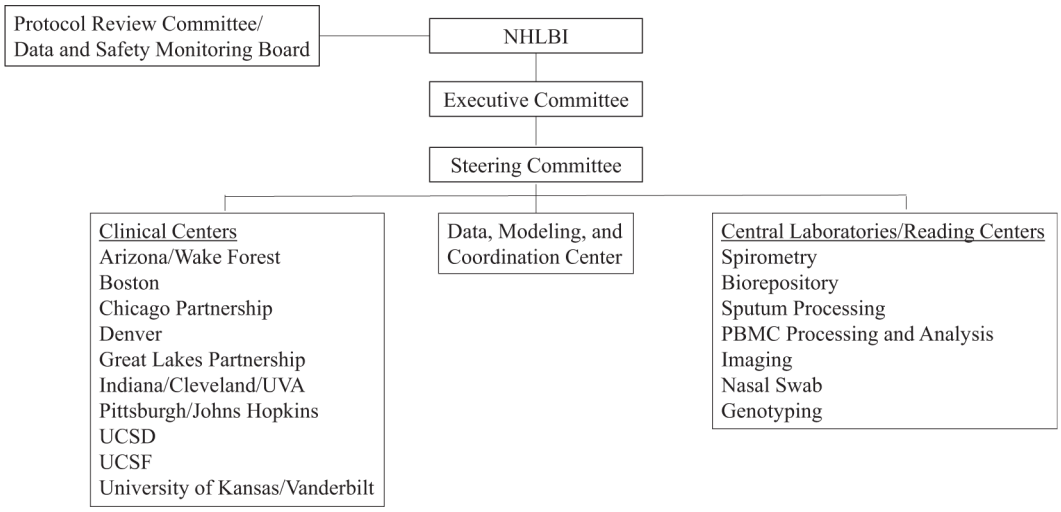

FIG 2.
Organization of the PrecISE Network.

Protocol Design Phase	Protocol Implementation Phase
Partnerships Committee	
Communication Committee	
Recruitment and Retention Committee	
COI and Ethics Committee	
Safety Committee	
Pediatrics Committee	
New Approaches Committee	
Publications and Presentations Committee	
Biomarker and Biospecimen Committee	
Biostatistics Committee	
Protocol Development Committee ⇨	Protocol Implementation Committee
Participant Advisory Committee	Adaptation and Design Committee
Resource Acquisition Committee	Quality Control Committee
T2 and non-T2 committees	

FIG 3.
Committees of the PrecISE Network. *COI*, Conflicts of interest.

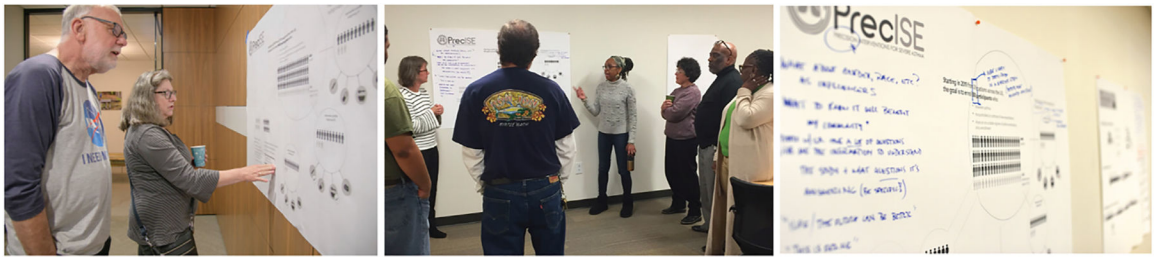

FIG 4.

Participant Advisory Committee. Large information graphics describing key aspects of the PrecISE trial (overview, randomization and procedures, visit structures) were posted on the walls to facilitate discussion and assist participants in quickly understanding the trial. Shared review and live annotation promoted robust and equitable discussion.

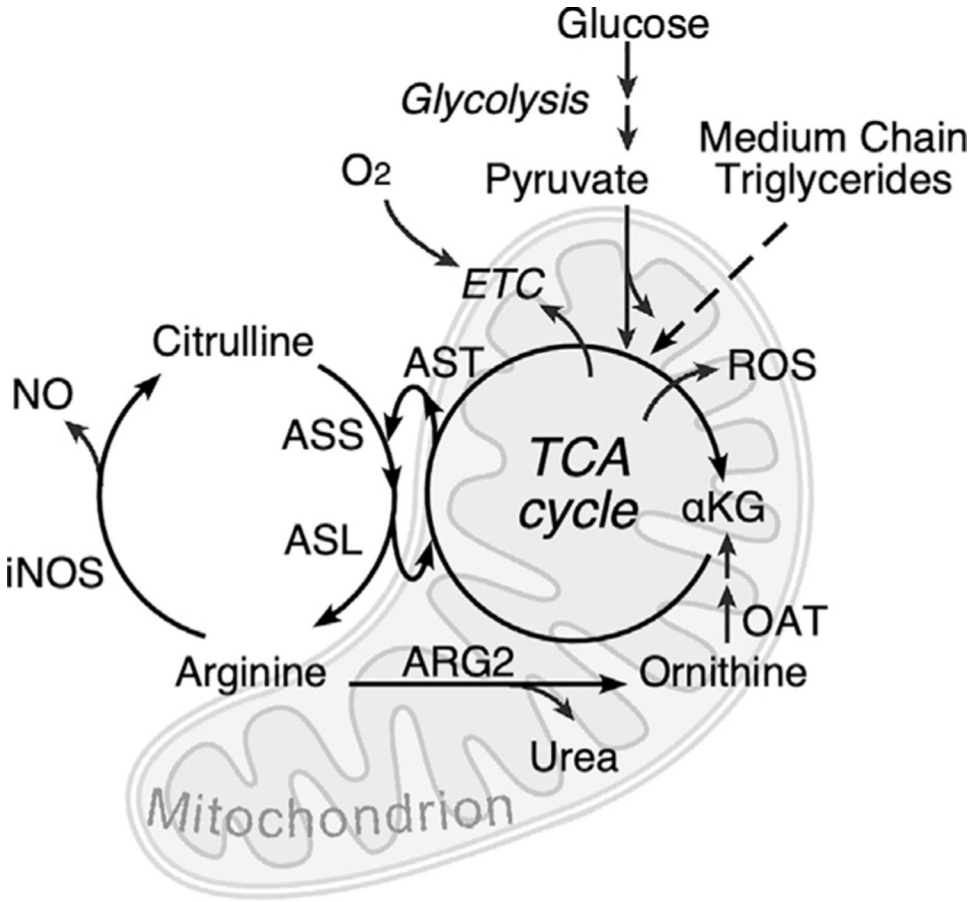

FIG 5.

Mitochondrial metabolism is connected through biochemical pathways with arginine/NO metabolism, which is a biomarker of asthma inflammation. The TCA pathway is linked to the arginine-citrulline cycle, which gives rise to NO. Arginase 2 (ARG2) is increased in asthmatic airway epithelial mitochondria, and feeds arginine into the TCA cycle via ornithine to alpha-ketoglutarate (aKG) to enter TCA and increase electron transport chain (ETC) for energy production. The acceleration of the TCA cycle leads to intermediates that dampen proinflammatory signal transduction. MCTs freely diffuse into the mitochondria, are oxidized rapidly, and feed acetyl-CoA into the TCA cycle. MCT may be protective against inflammation related to metabolism in those individuals with greater arginine metabolism as determined by FENO. *ASL*, Arginine succinate lyase; *ASS*, arginine succinate synthetase; *AST*, aspartate aminotransferase; *iNOS*, inducible NO Synthase; *OAT*, ornithine aminotransferase; *ROS*, reactive oxygen species. Reproduced with permission from Xu et al.59

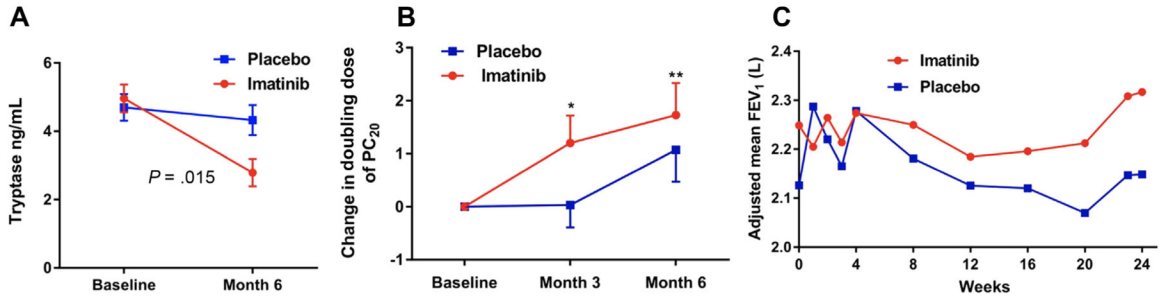

FIG 6.

Effect of the c-KIT inhibitor imatinib on (**A**) serum tryptase, (**B**) airway responsiveness, and (**C**) lung function in severe asthma. PC_{20}, Provocative methacholine concentration to cause a 20% decrease in FEV_1. *P = .03; **P = .008; P = .04 for difference in FEV_1.[98]

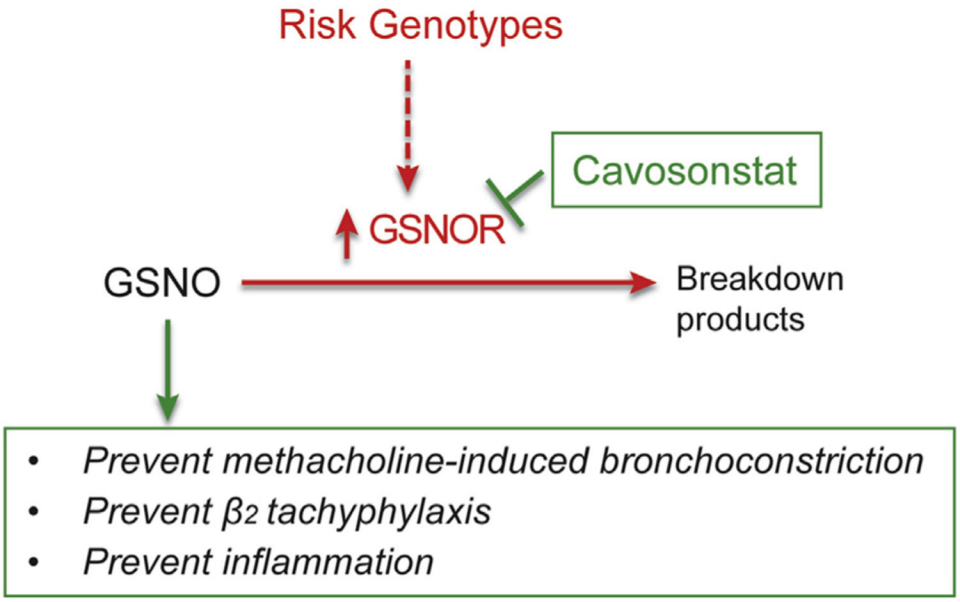

FIG 7.

The endogenous anti-inflammatory molecule GSNO is broken down by GSNOR in many patients with asthma. These patients can often be identified by genotype. Because of its effect to increase β2-receptor expression, it is anticipated that precision therapy with the GSNOR inhibitor, Cavosonstat, will improve β2 responsiveness in addition to improving lung function and reducing inflammation.

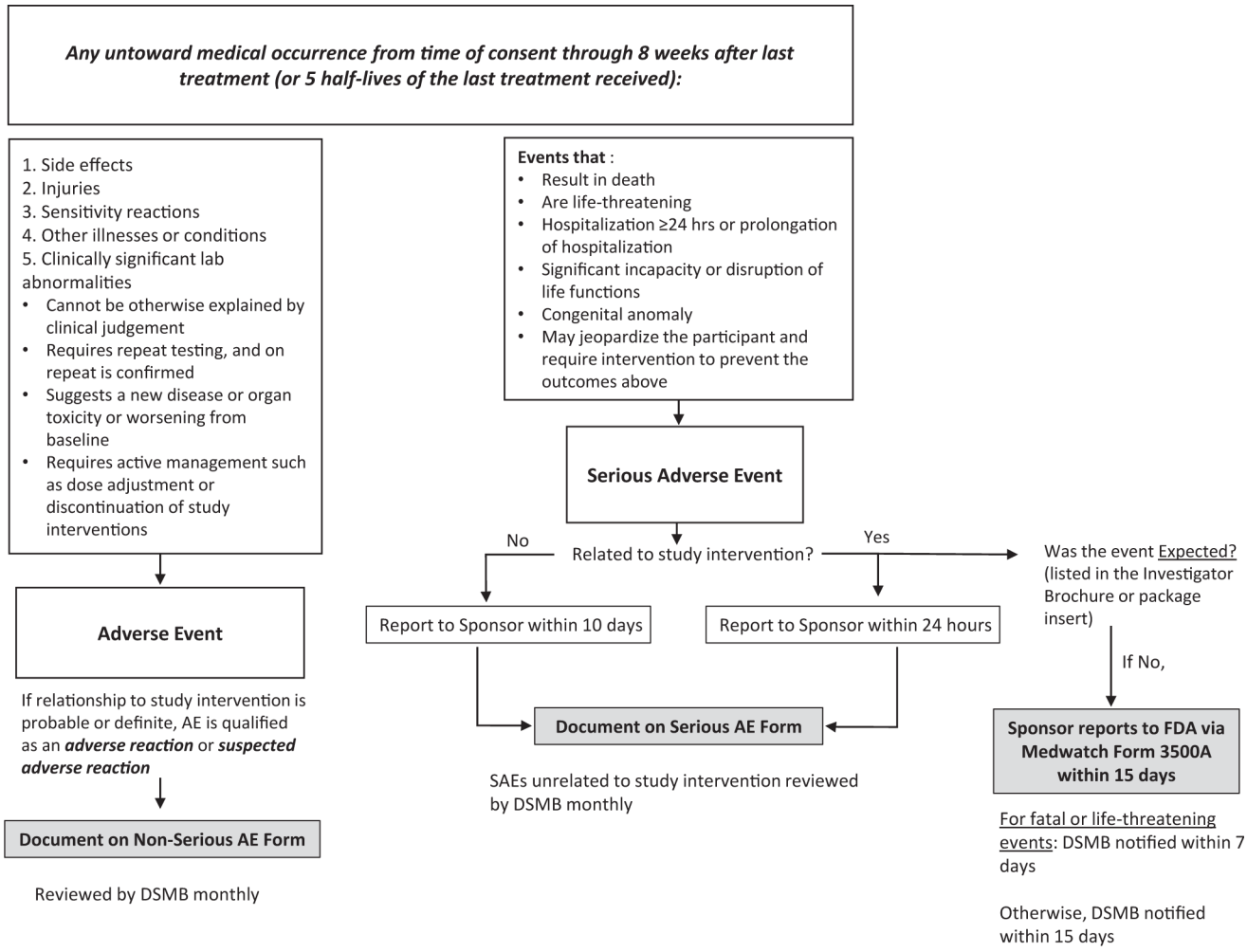

FIG 8.
PrecISE Network AE/SAE flowchart.

TABLE I.

Compounds and targeted subgroups

Compound	Drug target	Targeted subgroup	Estimated subgroup prevalence*
Imatinib	C-Kit	Eos < 300/μL	62%
Clazakizumab	IL-6	IL-6 > 3.1 ng/mL	33%
MCTs	Metabolic pathways	FENO > 15 ppb	64%
Broncho-Vaxom	Microbiome	Eos > 300/μL	38%
Itacitinib	JAK1/3	Eos > 300/μL or FENO > 25 ppb	53%

Eos, Eosinophils.

*Based on data from SARP

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TABLE II.

Key recommendations of the PrecISE Participant Advisory Group

Theme	Key recommendations
1. PrecISE study overview to identify points of interest, acceptability, and perceived benefits	*Engage participants in promoting the trial*
	1. Get statements/testimonials from others already participating in the trial, as this is a community that orients to others with the same lived experience
	Create communications that help participants get support for trial activities
	2. Provide explanatory materials for school officials that showcase the importance of the trial—"changing the future of asthma care"
	Close the loop with participants and their study data
	3. Provide participants and their personal physicians an end-of-study "debrief" that unmasks their treatments and how they did on each one
2. Study processes, such as randomizations, placebos, and washouts	*Make it easier for participants to complete the study*
	4. Make it possible/easy to transition between sites— college students away at school, snowbirds during the year, persons moving
	5. Determine way for adolescents of driving age to attend study visits alone
	6. Consider how to combine study visits with other MD appointments
3. Study procedures, such as schedules, tests, and incentives	*Improve feasibility and flexibility of study procedures*
	7. Consider shorter enrollment options with ability to "renew"
	8. Limit visit length to no longer than 3 h
	9. Provide flexible scheduling—early morning, nights, weekends. Schedule far ahead so participants can plan
	10. Allow surveys to be done at home or online
	11. Allow some tests to be performed at home (spirometry) or local facilities and sent to Clinical Center
	12. Provide school excuses for children, and "dean's" excuse for college students
	13. Ensure skilled technician for blood draws
4. Expected participant activities between visits, specifically medication tracking and logging	*Create multiple approaches for self-tracking*
	14. Paper diaries for participants who did not want to learn digital tracking or apps, or for older and minority participants who express significant concerns about data privacy
	15. Ensure parents and adolescents can share tracking data/logging—parents are looking for ways to safely transition adolescents to self-management
	16. Train coordinators how to troubleshoot and provide technical support for digital devices
5. Proposed treatments, including pathways and blinding	*Help participants incorporate treatments, prospectively address side effects*
	17. Create supports for use of medications at school

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Theme	Key recommendations
	18. Create materials with practical/specific advice for things participants can do to manage side effects (start medication on Friday night as it may cause diarrhea)
	19. Limit the number of injectable treatments for younger adolescents, as parents are tired of fighting to get kids to appointments for injections

TABLE III.

CompEx events

Diary variable	PEF (P) morning/evening	Reliever use (R) morning/evening	Symptoms (S) morning/evening
Threshold type	Decrease from baseline (%)	Increase from baseline (doses)	Increase from baseline (scores) or absolute maximum score
Threshold	15	1.5	1
Slope type	Decrease rate (% per day)	Increase rate (doses per day)	Increase rate (scores per day)
Slope	3	0.3	0.2

PEF, Peak expiratory flow.

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TABLE IV.

Exclusion criteria for screening laboratory studies in the PrecISE trial

Study	Exclusion threshold
Hemoglobin	<10 g/dL
Absolute neutrophil count	<1000/μL for Black participants
	<1500/μL for other participants
Absolute lymphocyte count	<500/μL
Absolute platelet count	<100,000/μL
Serum ALT/AST concentrations	>2× ULN
Serum bilirubin concentration	≥2× ULN
eGFR	<60 mL/min/1.73 m^2
HIV types 1 & 2 Ab/Ag immunoassay	Positive *
Serum hepatitis B surface Ag	Positive
Serum hepatitis B core total antibody	Positive
Serum hepatitis C antibody	Positive †
EKG	Significant clinical findings ‡
Serum QuantiFERON-TB Gold	Positive §

Ab, Antibody; *Ag*, antigen; *ALT*, alanine aminotransferase; *AST*, aspartate aminotransferase; *eGFR*, estimated glomerular filtration rate; *EKG*, electrocardiogram; *ULN*, upper limit of normal.

* A positive value is followed by a confirmatory test (Geenius HIV-1/HIV-2 antibody differentiation immunoassay); if result is positive, the participant is excluded.

† A positive value is followed by a confirmatory hepatitis C RNA test; if result is positive, the participant is excluded.

‡ As interpreted by an independent reader.

§ A positive test result requires further screening. A participant may be included in PrecISE if at least 1 of the following criteria is met:
- A chest radiograph done within the last 6 mo of the test that shows no evidence of active tuberculosis.
- A chest CT scan done within the last 6 mo of the test that shows no evidence of active tuberculosis.
- Documentation of adequate treatment for latent tuberculosis.