PrecISE: Precision Medicine in Severe Asthma: An adaptive platform trial with biomarker ascertainment

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Severe asthma accounts for almost half the cost associated with asthma. Severe asthma is driven by heterogeneous molecular mechanisms. Conventional clinical trial design often lacks the power and efficiency to target subgroups with specific pathobiological mechanisms. Furthermore, the validation and approval of new asthma therapies is a lengthy process. A large proportion of that time is taken by clinical trials to validate asthma interventions. The National Institutes of Health Precision Medicine in Severe and/or Exacerbation Prone Asthma (PrecISE) program was established with the goal of designing and executing a trial that uses adaptive design techniques to rapidly evaluate novel interventions in biomarker-defined subgroups of severe asthma, while seeking to refine these biomarker subgroups, and to identify early markers of response to therapy. The novel trial design is an adaptive platform trial conducted under a single master protocol that incorporates precision medicine components. Furthermore, it includes innovative applications of futility analysis, cross-over design with use of shared placebo groups, and early futility analysis to permit more rapid identification of effective interventions. The development and rationale behind the study design are described. The interventions chosen for the initial investigation and the criteria used to identify these interventions are enumerated. The biomarker-based adaptive design and analytic scheme are detailed as well as special considerations involved in the final trial design. (J Allergy Clin Immunol 2021;147:1594-601.)

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Key words: *Severe asthma, therapy, clinical trial, biomarkers, precision medicine, adaptive design, master protocol, platform trial*

Abbreviations used
FDA: Food and Drug Administration
PrecISE: Precision Medicine in Severe and/or Exacerbation Prone Asthma

GOALS OF PrecISE

Severe asthma is driven by heterogeneous molecular underpinnings. The new class of asthma biologics aimed at inhibiting type 2 inflammation is effective in only about half the patients with severe asthma.[1] Furthermore, the clinical response to these medications is highly variable. The development of new therapies takes many years, largely secondary to the time needed to complete clinical trials. Platform trials with adaptive study designs using master protocols are promising alternatives to conventional study designs due to their capacity to efficiently study multiple interventions. In addition, precision medicine approaches, using phenotypic "biomarkers" to identify subgroups of patients more responsive to the study intervention, are now available.

The National Institutes of Health Precision Medicine in Severe and/or Exacerbation Prone Asthma (PrecISE) program was established with the goal of creating a study that uses adaptive design techniques to rapidly evaluate novel interventions in biomarker-defined subgroups of severe asthma. In addition, the program seeks to refine the biomarker subgroups and to possibly identify early markers of response to therapy.

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As opposed to standard randomized trials in which the study procedures and outcomes are set at the beginning of the trial, and not modified after study initiation, adaptively designed studies allow prospectively planned modifications to 1 or more aspects of the design based on accumulating data from subjects in the trial and have been recognized as legitimate designs for drug approval by the Food and Drug Administration.[2] These adaptations are based on interim study data and have to be prespecified. Adaptive components can include 1, or several, of the following based on interim analyses: (1) Modifying allocation proportion to different arms; (2) Modifying the study population; (3) Modifying the end points; (4) Changing the sample size of the trial; (5) Dropping arms for futility; and (6) Stopping the entire trial early for futility or efficacy. Adaptive approaches allow for more efficient use of subjects because fewer subjects receive ineffective compounds and studies have the potential for producing results at smaller sample sizes than initially expected. In trials with multiple interventions, this results in more rapid changing of treatments and reassignment of resources to more promising candidates.

To achieve these aims, we designed a trial that incorporates an adaptive platform, a master protocol design, and precision medicine components. A platform design in a master protocol is a study designed in such a way that the basic structure can be used to perpetually evaluate multiple interventions for a disease process. Precision medicine approaches are adaptive approaches that allow for refinement of the patient subgroups targeted by interventions during a trial.

Although adaptive platform trials with precision medicine components have been used in cancer trials.[3,4] asthma is a temporally variable, complex, chronic inflammatory disease. Precision medicine trials in asthma present both opportunities and unique challenges for innovation in trial design. Herein, we describe the development and structure of the PrecISE platform trial (Clinical Trials.gov NCT04129931). It includes innovative applications of futility analysis, cross-over design, and use of a shared placebo to permit more rapid identification of effective interventions and refinement of predictive biomarker subgroups. Our goal is to acquaint the reader with the trial and the innovative tools and analytic approaches it uses. We outline our objectives in adopting different components of adaptation and study structure and the framework and rationale we developed to achieve these objectives. We also describe the criteria used to identify our potential interventions and the biomarker-based adaptive design and analytic scheme. In addition, we review special considerations relevant to the protocol and analysis, and implementation realities. A more detailed description of our statistical and analytic approach has been recently published.[5]

OBJECTIVES AND FRAMEWORK AND RATIONALE TO ACHIEVE OBJECTIVES

The Steering Committee and the Data, Modeling, and Coordination Center defined the objectives outlined in Table I. To achieve these objectives, we agreed on the following conceptual approaches based on the provided rationales:

1. Using a master protocol to allow more rapid introduction of potential interventions rather than designing new protocols for each drug.
2. Using a cross-over design with multiple periods in which subjects are treated with multiple interventions and the interventions share the same placebo for that subject, to maximally use information from recruited subjects. Such a design also provides subjects with an opportunity to "try" multiple interventions in the context of one overall trial.
3. Allowing interventions to demonstrate efficacy on any one of multiple efficacy outcomes (eg, exacerbations, airway function, and symptoms). Simultaneously testing for efficacy on multiple outcomes allows the use of the same trial design across interventions, even though we might be testing interventions that address different components of asthma pathobiology.
4. Reducing drug exposure time to the minimum duration thought to provide a likelihood of response to allow testing of multiple agents in a shorter time frame. For this reason, we adopted a substitute for exacerbations (CompEx) (see below) to evaluate efficacy in regard to exacerbations using a reduced intervention duration.
5. Performing an early futility analysis to reduce the time committed to testing of interventions with a lower likelihood of efficacy, thus allowing more rapid accrual to the remaining interventions and/or replacement of those ineffective interventions with "back-up" interventions.
6. Preferentially assigning subjects to interventions on the basis of prespecified biomarker thresholds to allow rapid assessment of whether a drug is effective in the prespecified biomarker subgroup.

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TABLE I. PrecISE objectives

Primary
1. To identify novel therapies that are efficacious in predefined biomarker-based subgroups of patients with severe asthma
2. To optimize the subgroups targeted for treatment by refining the biomarkers and subgroup definitions
Secondary
1. To gain information about potential monitoring biomarkers for selected therapies
2. To explore the safety and effectiveness of selected therapies in adolescent patients with severe asthma

7. Assigning some subjects to interventions even if they are outside the initial prespecified biomarker group to permit adjustment of biomarker thresholds during the study.

CRITERIA USED TO IDENTIFY THE TOP CANDIDATE INTERVENTIONS

Each clinical center application to join the network had proposed at least 3 specific interventions. At the initial Steering Committee meeting, all interventions were discussed and each was subsequently scored on the basis of following criteria: (1) scientific basis for potential efficacy in severe asthma; (2) definition of a target biomarker subgroup likely to respond to the therapy; (3) feasibility of drug acquisition and administration (oral, injection, etc); (4) cost of therapy (if not donated by industry); (5) known safety profiles and potential considerations in severe asthma; and (6) likelihood of obtaining approval for use in adolescents from the US FDA. Those that were deemed to be safe and potentially accessible, with the greatest overall scores, were then pursued as the initial group of candidate interventions to be further investigated. Those finally chosen are listed in Table II. The hypothesized mechanisms and pharmacology of these interventions will be detailed in future publications.

Each intervention required identification of proposed predictive biomarkers (up to 2) that would define the clinical subgroup, hypothesized a priori, to most likely respond to each intervention. Those chosen are listed in Table II. Several secondary and exploratory predictive biomarkers were also identified for each intervention. In addition to using biomarkers to predict intervention response, each intervention required proposed biomarkers that would serve as monitoring biomarkers, intended to help identify early signs of efficacy (or lack thereof) (Table II). Several additional interventions are being similarly assessed to serve as alternatives should any of the initially chosen agents be eliminated because of futility or safety concerns.

PROTOCOL DESIGN AND ANALYTIC SCHEME

The study aimed to randomize 800 subjects (650 adults and 150 adolescents [age 12-17 years]). The general structure of the study is summarized and illustrated in Fig 1. Briefly, over an approximately 8-week period, patients with reported asthma are screened to be sure they meet criteria for severe asthma.[6] During that period their biomarkers for all possible interventions are ascertained. Where possible, subjects' inhaled corticosteroid/long-acting β-agonist controller inhaler is changed to a standard high-dose inhaled corticosteroid/long-acting β-agonist combination. Baseline symptoms and lung function are measured, and safety labs are assessed. Based on a subject's biomarker profile, the intervention-specific safety measurement thresholds, the available interventions, and the progress of the study, subjects are randomized to their first intervention, with an increased probability (but not a certainty) that they will be randomized to a treatment "best" for them on the basis of their biomarker profile.

As illustrated in Fig 1, each period of treatment consists of 4 months of treatment and a 2-month washout (except for clazakizumab treatment, which requires a 4-month washout due to a long half-life). The first 2 periods of treatment correspond to a double-blind placebo-controlled 2-period cross-over design for the assigned intervention, such that a subject will receive placebo during 1 of the initial 2 treatment periods. These 2 periods were incorporated so that patients who are not able to participate after these first 2 periods are guaranteed to have a placebo period. After the initial 2-period cross-over, each participant continues with repeated rerandomizations to sequential 4-month treatment periods and 2- (or 4-) month washout periods, for up to a total of 4 additional treatments. In each of these subsequent periods, subjects are assigned to interventions or a matching placebo (~7:1 ratio during each period) on the basis of biomarker profile, their history of previous treatments including placebo, the intervention-specific safety measurement thresholds, and the overall enrollment in each of the interventions at the point of each rerandomization. As discussed in the next section, no subject will be randomized to more than 2 placebo periods during the trial.

Subjects enrolled at the beginning of this 42-month study can potentially receive a maximum of 5 different active treatments of the 6 listed in Table II (as long as none had a prolonged washout period). All subjects will have at least 1 required placebo (during the 2-period cross-over) and a maximum of 2 placebo periods.

The analytic approach and biomarker adaptation are illustrated in Fig 2. Specifics of the analysis plan and the thresholds used are discussed in our statistical design article.[4] Briefly, as illustrated in Fig 2, after 60 subjects are enrolled and complete an intervention in the prespecified biomarker-defined target subgroup, a futility analysis will be undertaken. If a drug is determined to be futile, that intervention is immediately discontinued, thereby freeing up patient resources to more rapidly complete investigation of other interventions or introduction of a new intervention with its attendant predictive biomarkers. If futility criteria are not met for the intervention, then a biomarker subgroup refinement is undertaken (see Fig 2) on the basis of outcomes in the 60 patients and 30 additional subjects who have been enrolled in that intervention outside the initial target subgroup. If necessary, the biomarker cutoff will be adjusted so that the next 45 subjects will be enrolled using the new threshold, with approximately 20 additional subjects enrolled outside the new target threshold. Once completed, a second biomarker subgroup optimization will be performed (see Fig 2), and a final 45 subjects will be enrolled in the new, refined target subgroup. Final efficacy analyses will be performed on the 150 subjects who were in the target subgroups at any point in the study (green band in Fig 2).

SPECIFIC CONSIDERATIONS REGARDING STUDY DESIGN AND ANALYSIS

The study design and analysis plan outlined in Figs 1 and 2 require several areas of explication.

TABLE II. PrecISE interventions and biomarkers

Investigative approach (agent)	Target population	Predictive biomarker & threshold	Exploratory monitoring biomarkers	Secondary & exploratory predictive biomarkers
Kit receptor inhibitor (imatinib)	T2 low	Blood Eos <300/μL	Serum tryptase Urinary PGD2	Serum tryptase Sputum PMNs Urinary PGD2 Sputum tryptase Airway wall thickness on HRCT Sputum mast cell gene expression
Anti–IL-6 (clazakizumab)	Obesity/metabolic dysfunction	Plasma IL-6 ≥ 3.1 pg/μL	hsCRP	hsCRP Fat density on HRCT
Jak inhibitor (itacitinib)	T2 high	Blood Eos ≥ 300/μL or FENO > 20 ppb	FENO Blood Eos	hsCRP Sputum eosinophils Plasma IL-6 Mucus score on HRCT
GSNO eeductase inhibitor genotype (cavosonstat)	Increased GSNOR activity by genotype	GSNOR genotype	EBC-formate to formaldehyde ratio	Change in maximal post-BD FEV_1 Air trapping on HRCT
Bacterial extract (Broncho-Vaxom)	Eosinophilic	Blood Eos ≥ 300/μL	Blood Eos Stool microbiome	Sputum eosinophils Mucus score on HRCT
Nutritional ketosis (medium-chain triglycerides)	High arginine metabolic asthma	FENO ≥ 15 ppb	Blood ketones	Urinary bromotyrosine Fat distribution on HRCT

BD, Bronchodilator; *EBC*, exhaled breath condensate; *Eos*, eosinophils; FENO, fractional exhaled nitric oxide; *GSNOR*, S-nitrosoglutathione reductase; *HRCT*, high-resolution chest computed tomography; *hsCRP*, high-sensitivity C-reactive protein; *ppb*, parts per billion; *T2*, type 2 inflammation.

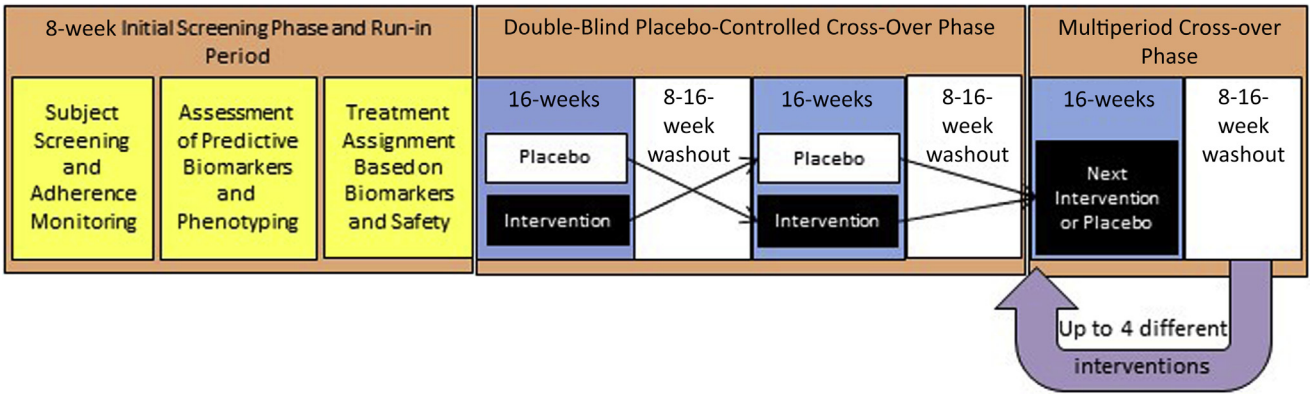

FIG 1. PrecISE study structure. See the Protocol design and analytic scheme section.

Outcomes

Because the study structure is designed to facilitate screening of multiple interventions with different mechanisms, the selected interventions may impact differing aspects of asthma control. We therefore chose 3 primary efficacy outcomes to address this possibility. Specifically, we chose to assess (1) airway function (FEV_1); (2) symptoms (Asthma Control Questionnaire – 6-question version); and (3) exacerbations and loss-of-control events as a substitute for exacerbations, using the CompEx instrument.[7] These outcomes will enable us to determine the effect of each intervention on the 3 key components of asthma morbidity. Importantly, we considered the possibility of including asthma exacerbations (defined as a treatment with systemic corticosteroids) as a primary outcome measurement. However, the sample size required to appropriately test a reasonable effect size prohibited using asthma exacerbations as a primary end point. Because of this limitation, the investigators elected to use the CompEx instrument as a substitute for asthma exacerbations. Steroid-requiring exacerbations will be examined as a secondary outcome, and safety measures will be in place to handle exacerbations. The effect sizes for a difference in treatment responses relative to placebo that we believe we will be able to detect with 80% power in a final sample of approximately 150 subjects within the target biomarker subgroups are listed in Table III. In all these calculations, data from adolescents will be combined with data from the adults.

Upfront assignment to interventions based on phenotypic biomarkers

We have predefined the initial "target" biomarker subgroup that we will test for each intervention as outlined in Table II. In this study, subjects who fall within the parameters of a biomarker-defined subgroup will be preferentially assigned to the intervention(s) expected to be effective for that biomarker profile (Fig 2). We point this principle out to contrast it with the typical *post hoc*

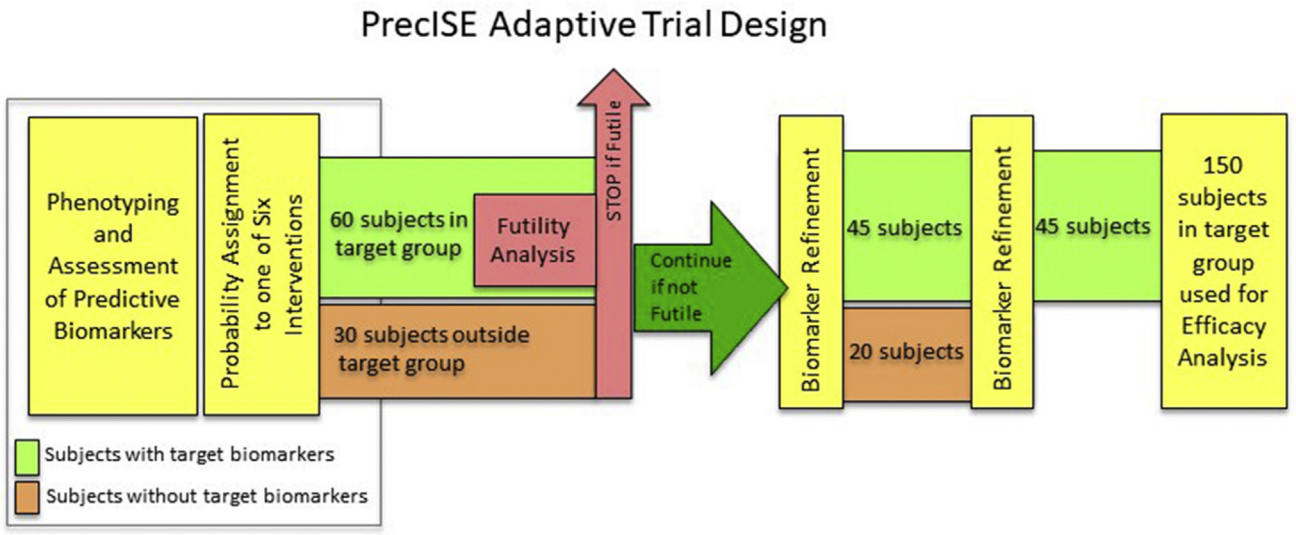

FIG 2. Futility analysis, biomarker adaptation, and study analysis for an intervention in PrecISE. Patients are characterized, and their biomarker characteristics are determined and assigned during the run-in (see text). On the basis of these biomarker characteristics (Table II), they are preferentially (but not exclusively) assigned to interventions and placebos throughout their participation in the trial (Fig 1). As seen in Fig 2, patients within the target biomarker subgroup (green band) and those outside the target subgroup (orange band) are assigned to each intervention. After an intervention has accumulated 60 patients within the target biomarker subgroup (green band) and 30 subjects outside the biomarker subgroup (orange band), a futility analysis is performed restricted to the within-target 60 patients (see text). If the intervention is dropped for futility, all patients still receiving that intervention are assigned to alternative interventions. If the intervention is not dropped for futility, subgroups are refined and subjects within and outside the newly refined biomarker thresholds are enrolled and evaluated as outlined with an additional scheduled refinement as shown. When 150 patients are enrolled within the varying refined subgroups, a final efficacy analysis is performed restricted to the 150 patients within the refined subgroups.

TABLE III. PrecISE primary outcomes

Primary outcome	Minimally detectable treatment difference from placebo (80% power)
Airway function (FEV_1)*	4.3% predicted
Symptoms (ACQ-6)†	0.3 score
Loss of asthma control (CompEx)‡	0.66 event rate

ACQ-6, Asthma Control Questionnaire – 6-question version.
*FEV_1 measured before bronchodilator administration (assumed SD = 14.5%).
†Asthma Control Questionnaire (assumed SD = 1).
‡CompEx (assumed SD = 2).

biomarker discovery approach. In the latter approach, subjects may be randomly assigned to therapies and *post hoc* analysis identifies biomarker profiles that associate with improved responses to specific therapies. In our case, we have initially prespecified the target biomarker subgroup for each intervention (Table II) and if an intervention is not found to be futile (after enrollment of the first 60 subjects in the target biomarker subgroup), we will refine the target biomarker group and assign additional subjects to the intervention (Fig 2). At this point, we continue to include some subjects outside the (newly) defined target subgroup, so that we can perform a second biomarker refinement step for the subgroup after additional patients have been enrolled (Fig 2). We will perform *post hoc* analyses to see whether we can identify other biomarkers that define responder subject subgroups. In Ivanova et al,[5] we consider the statistical implications of upfront adaptive assignment versus unbiased assignment in more detail.

As a corollary, we were faced with the issue of when to assign a subject's predictive biomarker characteristics. We have chosen to assign predictive biomarker status on the basis of biomarker determinations during the run-in period, before any treatment intervention. We have done so to decrease issues related to possible carryover effects from a previous treatment during the short interval of time available for the washout (see below 4-month intervention periods and 2-month washout, except for clazakizumab's 4-month washout). Although we will not be reassigning subject predictive biomarker status during the process of preferential randomization assignments, we will be reassessing these predictive biomarkers before each randomization period. In a secondary analysis, we will examine whether predictive biomarkers obtained just before each intervention period are better in defining target response subgroups.

Crossing subjects over to multiple treatments to maximize the information collected in the study

We adopted a cross-over design for multiple reasons: (1) Because the subject population is limited, crossing subjects reduces the need to recruit a new population for each intervention and increases power for the sample size because each subject is used as their own control. (2) Because subjects may qualify for multiple interventions based on overlapping target subgroup definitions, crossing subjects over from one treatment to another affords subjects the opportunity to be assigned to multiple drugs with a greater opportunity to identify interventions effective in a particular subject (in effect "precision" medicine at the subject level within the context of the trial). (3) Multiple cross-overs allow us to "share" placebo periods, providing increased

efficiency to compare an intervention with placebo (see later Placebo Considerations).

Early futility analysis and futility boundaries

All of our currently proposed interventions are novel in severe asthma. Many have not been tested in humans as regards their efficacy in severe asthma. Thus, there is a likelihood that several may be ineffective. We recognized that enrollment of a full cohort along with biomarker profiling specific to an intervention that was not effective (as judged by our outcomes in our trial) would divert subjects and resources from potentially informative interventions. To make the trial adaptive in this regard, we strove to introduce early futility analysis. Furthermore, we set moderately wide boundaries in these analyses (please see Statistical Analysis Publication[5]). We recognized that setting wider futility boundaries may result in a higher likelihood of discontinuing "effective" therapies, and therefore tried to balance this consideration against our goals of testing multiple interventions.

Four-month intervention periods and 2-month washout

The study timelines allow us a maximum of 42 to 44 months of study participation to have a sufficient number of cross-over treatments per subject to meet our study objectives. We designed a 4-month treatment period and a 2-month washout period for each intervention. Our rationale for choosing 4 months and 2 months is as follows: (1) Nearly all effective asthma treatments to date have shown most of their effect within 3 to 4 months. (2) Although effects on yearly exacerbations cannot be assumed to be reflected accurately within 4 months, we are using the recently reported instrument known as the CompEx, which, with 3 months of measurement, generally yields similar power to that obtained measuring annual asthma exacerbation rates over a year.[7] (3) As regards the washout, 2 months exceed 5 times the known pharmacokinetic half-life of the drugs under consideration (except for clazakizumab, for which we introduced a 4-month washout period). In regard to this latter point, we recognized that it is possible that the pharmacodynamic half-life of an intervention could exceed the 2-month washout. To account for this possibility, we are not assessing efficacy (at the end of each period) relative to baseline at the start of each period, but rather comparing interventions with placebo on the basis of outcomes measured at the end of each treatment period. To assess whether our washouts are long enough, we will model baseline efficacy outcomes as a function of previous treatment to shed light on the presence of carryover effects in the trial.

Placebo considerations

To assess whether an intervention is effective within its biomarker subgroup, interventions will be compared with a placebo administered during the double-blind placebo cross-over phase (Fig 1) and additional placebos administered during subsequent treatment assignments. The latter additional placebos have been inserted to preserve blinding in the subsequent periods, and to assess for period, seasonal, and secular temporal effects over this approximately 3.5-year study. As described in the Protocol design and analytic scheme section, after the initial double-blind 2-period cross-over period, subjects will be randomized to active intervention or matching placebo at an approximately 7 to 1 ratio, with the caveat that no subject can receive placebo in more than 2 periods during the trial. Throughout the trial, subjects assigned to placebo will receive a single dummy appropriate to their assigned therapy for that period. We did not introduce simultaneous dummies for all the interventions (potentially up to 6 interventions and dummies at the same time) due to subject burden.

IMPLEMENTATION REALITY AND CHALLENGES OF DEVELOPING A PLATFORM PROTOCOL

Implementation of our design has presented several challenges.

Drug acquisition

Because almost all our therapies are novel interventions in asthma, most of these drugs are not available for purchase over the counter. As a result, we needed to negotiate with each manufacturer to obtain drug. All the manufacturers were interested in participating, but contract negotiations related to intellectual property and drug manufacturing timelines frequently caused delays. In some cases, production of placebo has also contributed to delays. At the time of this writing, we have reached agreement with manufacturers of all 6 initial interventions but some of these negotiations have taken more than a year.

Regulatory approval

Almost all of our interventions are investigational new drugs (not currently on the market) or not approved for use in asthma and therefore require FDA approval for study in severe asthma. The FDA agreed that we could submit a single Investigational New Drug Application for the PrecISE master protocol that included all interventions available at study start, with Investigational New Drug Application amendments submitted as other interventions are added to the study. The FDA also gave us guidance that to approve interventions for adolescents, the intervention would have to have minimal toxicity or, if there were potential for toxicity, we would need to show adequate evidence to suggest effectiveness in severe asthma. As a result, of the 6 interventions listed in Table II, it appears at this time that only 2 will be able to be used in adolescents.

On the basis of availability, we have initiated the trial with medium-chain triglycerides and clazakizumab. At the time of this writing, we have received FDA approval to add imatinib. Approval to add cavosonstat, Broncho-Vaxom, and itacitinib will hopefully follow in short order.

Overlapping target biomarker groups and prevalence of the target biomarker group in the population

Some of the interventions chosen have overlapping biomarker-defined target subgroups as can be seen in Table II. We realized that if we attempted to enroll subjects in these interventions simultaneously, accrual would be slow and thus a futility analysis would be delayed. As a result, if a subject is eligible for 2 or more interventions, the randomization algorithm favors the intervention closest to achieving the enrollment target for the first interim analysis (the futility interim analysis).

CONCLUSIONS

The PrecISE trial represents an innovative approach to trial design in severe asthma. By bringing together experts in clinical trial design, adaptive trial design, and development of master protocols, we have developed a platform that we believe will allow us to rapidly evaluate novel interventions in severe asthma. The design also simultaneously allows us to define and refine potential predictive biomarkers and to explore biomarkers of response. The trial structure also permits subjects to receive multiple interventions with reduced placebo periods, making the approach more attractive to potential participants.

REFERENCES

1. Israel E, Reddel HK. Severe and difficult-to-treat asthma in adults. N Engl J Med 2017;377:965-76.
2. US Food and Drug Administration. Adaptive designs of clinical trials of drugs and biologics: guidance for industry. Docket Number FDA-2018-D-3124. Silver Spring, MD: US Food and Drug Administration. 2019. Available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/adaptive-design-clinical-trials-drugs-and-biologics-guidance-industry. Accessed January 14, 2021.
3. Park JW, Liu MC, Yee D, Yau C, van't Veer LJ, Symmans WF, et al. Adaptive randomization of neratinib in early breast cancer. N Engl J Med 2016; 375:11-22.
4. Rugo HS, Olopade OI, DeMichele A, Yau C, van't Veer LJ, Buxton MB, et al. Adaptive randomization of veliparib-carboplatin treatment in breast cancer. N Engl J Med 2016;375:23-34.
5. Ivanova A, Israel E, LaVange LM, Peters MC, Denlinger LC, Moore WC, et al. The precision interventions for severe and/or exacerbation-prone asthma (PrecISE) adaptive platform trial: statistical considerations. J Biopharm Stat 2020; 30:1026-37.
6. Chung KF, Wenzel SE, Brozek JL, Bush A, Castro M, Sterk PJ, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. Eur Respir J 2014;43:343-73.
7. Fuhlbrigge AL, Bengtsson T, Peterson S, Jauhiainen A, Eriksson G, Da Silva CA, et al. A novel endpoint for exacerbations in asthma to accelerate clinical development: a post-hoc analysis of randomised controlled trials. Lancet Respir Med 2017;5:577-90.