Institutional Review Board
Informed Consent Document for Research
(Adult)

Study Title:	**PrecISE: Precision Interventions for Severe and/or Exacerbation-Prone Asthma Network**
Version Date:	**04/08/2022**
Version:	**4.1**

Part 1 of 2: MASTER CONSENT

Name of participant: _____ Age: _____

You are being invited to take part in a research study called the PrecISE study. This study is a multi-site study, meaning that subjects will be recruited from several different locations. Because this is a multi-site study, this consent form includes two parts. ***Part 1 of this consent form*** *is the Master Consent and includes information that applies to all study sites.* ***Part 2 of the consent form*** *is the Study Site Information and includes information specific to the* ***study site*** *where* ***you are being asked to enroll****.* ***Both parts together are the legal consent form and both parts must be provided to you.***

If you are the legally authorized representative of a person who is being invited to participate in this study, the word "you" in this document refers to the person you represent. As the legally authorized representative, you will be asked to read and sign this document to give permission for the person you represent to parti cipate in this research study.

This consent form describes the research study and helps you decide if you want to participate . It provides important information about what you will be asked to do during the study, about the risks and benefits of the study, and about your rights as a research participant. By signing this form, you are agreeing to participate in this study.

This consent will either be conducted in-person or remotely (by phone or video conference call). We will follow the same procedures and regulatory guidelines regardless of the method used to obtain your consent.

This study involves multiple different types of potential treatments. You will be asked to review information for each study treatment to learn more about its risks and benefits. The current list of possible study treatments is below in Table 1, and more detailed information about these treatments is included later in this consent form. The PrecISE study will begin with two treatments, but we expect to add more as the study continues. If new treatments are added to the study later on, you will be asked to review information about the new treatments and consent to those separately. **If you choose not to consent to the new treatments when they are added to the study, your participation with the current treatments will not be affected.** Before signing this master consent form:

- You should read this entire consent form carefully.
- Only sign this form if you are willing to participate in all possible treatments and procedures.
- You should review the information for each available study treatment and required procedures before signing this consent form. You will not be able to choose which treatment you are assigned to or which procedures you want to do. You will have the opportunity to review information on any new treatments and procedures that might be added to the study later once they are available.
- If you have any questions about anything in this form, you should ask the research team for more information.
- You may also wish to talk to your health care provider, family or friends about your participation in this study.

- Do not agree to participate in this study unless the research team has answered your questions and you decide that you want to be part of this study.

KEY INFORMATION ABOUT THIS STUDY

PrecISE is a multi-site study, sponsored by the National Heart, Lung, and Blood Institute. We are inviting people to participate in PrecISE who: 1) are age 12 or older, 2) meet guideline criteria for severe asthma, 3) currently have uncontrolled asthma, or continue to have exacerbations (attacks), and 4) are on a stable regimen of asthma medications (controller/daily medication). We will find out if you qualify for the study after you finish the screening tests.

This study is designed to investigate new treatments for asthma that are thought to work better in some patients than in others. The data from this research study will be used to determine which treatments work and what kind of patient benefits the most from that treatment.

If you choose to take part in the study, you can receive several different treatments depending on when you begin the study. You will take each treatment for about 4 months, and then take a break for 2 to 4 months, before starting another treatment. You will take study treatments in addition to your current (or study provided) controller medication. The study will run for about 3 ½ years, and most of the people participating in the study will go through 2-3 different treatments before finishing the study.

As part of your study participation, you will be randomly assigned (by chance like rolling dice) to a treatment (also called an ***intervention***) at different times during the study; this is referred to as 'randomized'. You will not be able to select the treatment, and you may be excluded from certain treatments due to safety concerns and other considerations. Some of the periods will involve a placebo instead of the active therapy. Once you have been randomized, the treatment assignment cannot be changed until the treatment period ends and you are randomized again. The current drugs under study are listed below. There may be more added in the future.

Table 1. List of possible treatments

Treatment	Brief Description
medium chain triglycerides (MCT)	Food supplement, powder, similar to protein powder, that can be mixed with food or water
clazakizumab, an anti-IL6 treatment	Biologic* given as a monthly shot (4 times)
imatinib	Drug given as oral capsules
Broncho-Vaxom	Drug given as oral capsules
cavosonstat	Drug given as oral capsules

* A biologic drug is a product that is produced from living organisms or contains components of living organisms.

Participation in this study will involve various procedures including a physical exam, blood draws, different lung function measurements, surveys and an optional CT scan or x-ray. The procedures will be conducted during visits to the clinic, but some procedures, such as spirometry may also be done at home. Due to the COVID-19 pandemic, not all procedures will be conducted at all clinic visits.

Possible risks or discomforts from these procedures may include, but are not limited to: bruising or other reactions from blood draws, dizziness, shortness of breath and coughing during lung function tests, and radiation exposure during the optional CT scan or chest x-ray.

Good effects of this study include possible direct benefits to you from one or more of the study treatments and benefits to science and humankind.

There are alternatives to participating in this study, including getting standard treatment from your doctor, participating in other studies, and/or electing to take one of the recently approved drugs for asthma, instead of the treatments being offered on this study.

You do not have to be in this research study. You may choose not to be in this study and get other treatments without changing your healthcare, services or other rights. You can stop being in this study at any time. If we learn something new that may affect the risks or benefits of this study, you will be told so that you can decide whether or not you still want to be in this study.

The purpose of PrecISE is to find new treatments for severe asthma by using a novel approach in medicine called precision medicine. Precision medicine is a method that tailors, or customizes, medicines to patients based on their biomarkers. Biomarkers are bits of information about you, based on the results of different tests, for example, blood tests, analyses of your breath, and genetic tests. By using your biomarkers and evaluating different treatments in the study, we hope to learn more about treatments that are tailored to individuals and their needs.

This document uses words such as treatment and medication. Please remember this is a research study and the use of these words does not mean that the treatments have been found to be effective for asthma.

WHAT WILL HAPPEN IN THE STUDY?

During your first two months in the study, we will check to see if you qualify for randomization to a treatment. If you are eligible, you will then be randomly assigned to a treatment and will begin your first *treatment period*. As noted above, some of the periods will involve a placebo instead of the active therapy. A placebo looks like the active treatment but doesn't contain active ingredients. You will receive placebo in at least one of your treatment periods. You might receive placebo in one or two more treatment periods after that, but you will never have to complete more than two 16-week placebo periods total.

If you agree to be in the study, you will participate in at least 2 treatment periods, each followed by an 8- or 16-week washout period, for a total of 12 – 14 months. A washout period is the time between treatment periods. Instead of immediately stopping and then starting the new treatment, there will be a period of time where the treatment from the previous period is washed out of your system. You will not take any study treatment during the washout. The total number of treatments you will be eligible to receive will depend on when you enroll in the study.

Study visits are described in more detail below and a detailed *Schedule of Study Visits* is provided at the end of Part 1 of this document. The possible risks of each study procedure are described in a section below entitled "WHAT ARE THE RISKS OF THIS STUDY?"

Screening Visit(s) - (*Can be completed over multiple visits if necessary)*
Before any study information is collected, a member of the study team will review this master consent with you and will make sure to answer any questions that you have about participation in this study. Consent review may take 1 to 2 hours, depending on the questions you have about the study. If you agree to participate in the study and sign this master consent form, you will complete a screening visit to determine if you continue to be eligible for the study. In some cases, the screening visit may be split over two or three study visits.

The screening visit(s) will include the following:
Consent: You will review and sign this master consent, if you agree to participate.
Physical Exam: Medical personnel will perform a physical exam on you, and an assessment of your general health, skin, eyes, ear/nose/throat, heart, chest, abdomen, and extremities. Your blood pressure, heart rate, respiratory rate, and temperature will be measured.
Questionnaires: You will complete several questionnaires where you will be asked to provide basic information about yourself and your past and current medical and surgical history, past and current medications, asthma symptoms and past exacerbations.
Pulmonary Function Testing:

- *Medication Withholds:* Before you come in for the baseline spirometry test, you will be asked to withhold some of the medications you currently take to treat your asthma, however, you should take your medications if you feel you cannot withhold, and tell us that when you are at the visit.
- *Spirometry:* You will be asked to take a deep breath in and blow your breath out as hard and fast as you can into a machine for at least 6 seconds. The machine measures the amount of air you can blow out and how fast you can blow it out. We have you do this 3 or more times so we can get an accurate measure of your lung function.
- *Maximum Bronchodilator Response Test:* After you perform the baseline spirometry you will take 4 puffs of albuterol to open your airways. You will then repeat spirometry 10-15 minutes later. The test will continue by having you take 2 more puffs of albuterol and then repeat spirometry 10-15 minutes later to see if your airways have opened as much as possible. You may be given 2 more puffs of albuterol and repeat spirometry again. You will receive no more than 8 total puffs of albuterol.
- *In-home spirometry*: You may also be given a home spirometer to do your breathing tests at home. The same procedures used to measure your breathing in the clinic will be used to measure your breathing at home. A staff member from the clinic will call you to talk about the procedures and coach you during the testing while you are at home.
- *Methacholine Challenge (if necessary)*: The methacholine challenge will be used to determine your asthma status if your breathing does not change enough during the maximum bronchodilator response test. Methacholine is a chemical that can cause the airway tubes to tighten and can bring on asthma symptoms. People who have asthma have airways that are sensitive to smaller amounts of methacholine than people without asthma. This test measures how sensitive your airway tubes are to the methacholine. We will measure your lung function before methacholine and after each dose of methacholine. You will be asked to breathe methacholine aerosol for 60 seconds, given through a nebulizer, starting at a very low dose. Your lung

function will be measured 30 seconds and 90 seconds after each dose of methacholine, if your lung function has not decreased by 20% the amount of the next dose is increased. The challenge will be stopped when your lung function measurements have decreased 20% from your baseline or you receive the highest dose we are using in the methacholine challenge. This test takes approximately one hour.

- *Lung Diffusion Capacity Testing (*DLCO*): If needed, based on smoking history*, you will do Lung Diffusion Capacity Testing (DLCO). The DLCO measures how well your lungs transfer oxygen to your blood. You will blow into a tube that is connected to a machine that measures air volumes. You will be asked to take a breath in, to exhale gently until your lungs are empty; to take as deep a breath in as you can, to hold your breath for 8-10 seconds, and to exhale gently.

Safety Labs:

- *Urine*: If you are a female who can become pregnant, you will provide a small amount of urine on all visits to make sure you are not pregnant before taking any study treatment or doing specific study procedures. You will not be enrolled if you are pregnant or breastfeeding. If you become pregnant during the study, we will ask that you let us know. If you are a woman who can get pregnant, you will need to use regular and highly effective birth control while in this study. Your study team will tell you what birth control methods are acceptable.

Peak Flow Meter, Home Spirometer, and sensors to attach to your controller medication and a rescue inhaler: You will be given a device called a *peak flow meter* and *sensors* to attach to your controller medication and rescue inhaler and asked to use them at home throughout your participation in the study. You will use the peak flow meter to obtain peak flow measures at home twice a day. The sensors will be used to monitor your day-to-day medication use. We will show you how to use these devices. Your compliance with these devices is very important and will be a factor in determining your eligibility to continue in the study. The sensors on your inhalers will collect the time, date, and approximate location of inhaler medication use. You may also be given a home spirometer to do your breathing tests at home.

Controller and Rescue Medication: As part of this study, you can receive controller and rescue medication, if you choose to do so, free of cost, and if available at the time of your enrollment. A controller medication is a long-term maintenance medicine that works over a period of time to ease airway inflammation and help prevent asthma symptoms. A rescue medicine is a fast-acting medicine that works immediately to relieve asthma symptoms when they happen. The study will provide the Advair Diskus as controller medication and a rescue (albuterol sulfate) inhaler. You can choose to stay on your current controller medication as long as it is approved by our study coordinator. In this case you will be responsible for purchasing it. The study coordinator will review medication administration and answer any questions you have. During subsequent visits, you will be asked to bring back your controller and rescue inhalers (study provided medication and medication that you obtain on your own) to each visit, even if empty. The sensors mentioned above will be used to monitor your daily controller medication and rescue inhaler use using the smartphone app described below. Please remember that continuing maintenance therapy (controller medications) is very important. If you choose not to take the study supplied medication, we will confirm that you are taking another approved controller medication throughout your time on the study. Please see below for additional information regarding the controller and rescue medication.

Application (App) Installation on Smart Phone (e-Diary): During the Screening Visit, study staff will help you install an app onto your electronic device (e.g. smart phone or tablet). This app (developed by the company Propeller Health) will be used as a diary to answer some questions about your symptoms. It will also record your home peak flow measurements and your use of controller medications, described above. This will be done twice a

day, in the morning and evening. In order to participate in the study, you must have or get a device such as an iPhone, iPad or iPod, or a smartphone or tablet that will allow you to download and use this app. Please note that data charges may apply by using your device to record information in the diary. The data will be transmitted daily to the company Propeller Health through this app and then to a secure server at the University of North Carolina at Chapel Hill.

When the Propeller Health app is first set up, it will collect the following information: name, date of birth, email address, medications, medication schedule for controller medication, time zone and phone number. You will also be asked to provide your gender, race, height and weight in order to accurately record the results of your breathing tests. Once permission is granted on the smartphone, the app will also collect information on your location. These data will be stored on Propeller's secure servers. At the end of the study, all identifiable data will be deleted. Propeller Health is interested in better understanding the management and impact of respiratory disease. Propeller may use your personal identifiable information (PHI) to create aggregated health information and de-identified data to improve their services and for public health.

You may also be asked to complete a paper diary or a web survey twice a day to record your data. The web survey will be on a website that is managed by the company called Qualtrics. If you are asked to complete the diary questions via a Qualtrics survey, you will receive the survey link via text. Standard text messaging rates will apply to these texts. In order to send these texts, your phone number will be stored on Qualtrics' secure servers. The same information collected on the survey will be sent to the University of North Carolina at Chapel Hill and will be stored on secure servers.

To use the home spirometer, we will be using an app (developed by the company ZEPHYRx) to record your breathing tests and to allow the study staff to coach you (via videoconferencing) and assess your breathing maneuvers. This app collects the following information: date of birth, gender, height, weight and ethnicity, which is used to calculate the pulmonary function test results. The same information collected on the app will be sent to the University of North Carolina at Chapel Hill and will be stored on secure servers.

DISCLOSURE OF IDENTIFIABLE INFORMATION IN THE EVENT OF AN ISSUE WITH YOUR PROPELLER HEALTH DEVICE. Propeller Health has a legal obligation to maintain records regarding complaints and incidents related to their device which includes both the sensor and the application. In the event that a patient has a complaint or there is an incident related to the device, Propeller Health may collect identifiable information regarding the complaint or incident for their records. This information can include the patient's name, contact information, device ID, and information related to the complaint or incident.

Asthma action plan: during the Screening Visit, study staff will explain to you an "asthma action plan" that you will use during the study. This plan explains what to do in case your asthma worsens while taking any of the interventions (drugs) or in-between these interventions. We will provide you with a printed instruction sheet and review this with you, and it will explain when to use albuterol rescue medication, when to call '911' or go to an emergency room or urgent care center, and when and how to contact us. We will also provide you with a printed card that will have contact information that an emergency doctor can use to contact us if needed.

Lifestyle Considerations: In order to be eligible for the study, you must comply with the following lifestyle considerations, throughout the duration of the study:

- Do not use tobacco products and nicotine containing products (including e-cigarettes, patches).
- Do not use inhaled marijuana.
- Do not use any illegal drugs including abuse of prescription drugs.
- *For females who can become pregnant*: you must use a highly effective form of birth control. This is described in more detail under the Risks section, below.
- Males, who are sexually active with a female who can get pregnant, must agree to use a medically acceptable form of birth control, such as barrier protection, as determined by the study doctor.
- Contraception should be used for at least 1 month prior to screening, throughout study participation and for an additional 16 weeks after the end of the final test treatment.

Run-in Visit

The run-in visit will occur 4-6 weeks after the Screening Visit and will confirm your final eligibility for the study. It will be the last visit before you are randomized into the first treatment period. The run-in visit will take approximately 4 to 5 hours and can be completed on more than one study visit.

The run-in visit, which may be split into several visits, will include the following:

Eligibility: Your eligibility will be re-assessed and confirmed.

Peak Flow Meter and e-diary Compliance: The study coordinator will review and discuss your compliance with the e-diaries and peak flow meters.

Controller Medication: The study coordinator will review and discuss your compliance with your controller medication. You will receive more controller and rescue medication, if applicable.

Physical Exam: You will receive a brief physical exam which may be done at the run-in or at one of the other visits prior to receiving your medications.

Questionnaires: You will be asked to update information about current medications and asthma symptoms and to provide us with information on any exacerbations that occurred between visits. You will also be asked about current medical conditions and any new symptoms.

Safety Labs: Blood, Urine and EKGs

- Blood and urine will be taken to establish and monitor your health and to potentially exclude you from certain treatments if we feel they would be unsafe for you. Please see the Table 3 at the end of this consent Part 1 for the amount of blood we will take at each visit.
    - With these labs, we will be looking at your blood cells, evaluating your liver function, and looking for any signs of abnormal test results. In addition, because some of the treatments might alter the normal function of your immune system, it is important to rule out certain viruses, such as hepatitis, HIV, and other infections, such as tuberculosis.
    - Blood will either be shipped to the study's Central Lab, Pharmaceutical Product Development (PPD), for analyses, or analyzed at Labcorp. After analysis is complete, any remaining blood will be destroyed.
    - Urine will be tested directly by dipstick at the clinical sites.
    - You will be informed of abnormal test results so that you can follow-up with your primary healthcare provider.
- Urine will be taken to assess pregnancy status on women who can become pregnant.

- An EKG is a tracing of the heart's electrical activity and it is used to look at the pattern of your heartbeat. It requires small wires being attached to your skin using small adhesive patches on several locations on your body. The EKG takes about 15 minutes.

Biomarkers: Biomarkers help researchers decide the type of asthma you have, if the treatment is working or if certain biomarkers will predict whether a treatment would work for you. Biomarkers will be collected via blood, nasal swab, sputum, urine, and a breathing test called fractional exhaled nitric oxide (FeNO).

- *Blood Biomarkers:* Blood will be drawn to collect and assess your biomarkers. See Table 3 at the end of this consent Part 1 for the amount of blood we will take at each visit. Some of the blood drawn will be used for genetic testing. Some of the blood will be used to isolate RNA from your blood cells. The rest will be used to measure for a variety of proteins and other molecules in your blood that will help researchers decide if the treatment is working or if certain biomarkers will predict whether a treatment would work for you.
    - In order to participate in this study, you must agree to genetic testing. For example, a specific type of genetics test, S-nitrosoglutathione (GSNO) genotyping, will be performed to provide information on your biomarkers. The DNA that will be used for this test will normally be obtained at the run-in visit. Occasionally, however, a DNA sample will not be useable for a variety of technical laboratory reasons, and we may ask you to provide an additional sample at a later visit, if the first DNA sample does not produce usable results. Additional specific genotyping will provide information on other biomarkers in PrecISE. Any genetic testing for use outside of the PrecISE study is optional, and you will be asked to agree to this below.
- *Exhaled nitric oxide (FeNO):* You will gently blow air out into a nitric oxide machine for 10 seconds. The nitric oxide machine will measure the amount of nitric oxide in your breath. Nitric oxide is a gas that is released from inflammatory cells in the lung.
- *Induced Sputum:* You will be asked to breathe in a salty mist for up to 12 minutes and to cough deeply and vigorously every two minutes in order to bring up a sample of sputum (mucus) from your lungs. Before the procedure you will be given 4 or more puffs of an albuterol inhaler to protect against the bronchospasm (tightening of the bronchial tubes) that can occur from breathing in a salty mist.
- *Nasal swab:* We will use a small, sterile, disposable nasal swab, to collect cells and secretions from your nasal cavity to measure biomarkers of inflammation in your nose.

Pulmonary Function Testing:

- *Spirometry (as described above)*
- *Spirometry POST 4 puffs albuterol:* You will take 4 puffs of albuterol to open your airways. You will then repeat spirometry (as described above) 10-15 minutes later.
- *Medication Withholds (as described above)*

CT Scan: The CT scan is a special type of x-ray examination. You will be asked to lie on a table with your arms resting above your head. You will need to remain still and hold your breath for about 10-20 seconds during each scan. You will then be asked to breathe out and hold your breath again and the scan will be repeated. If you are a woman who can become pregnant, you will have a pregnancy test to make sure that you are not pregnant before having the CT scan. Due to scheduling constraints, the CT scan may be conducted before you have completed all of the study's eligibility assessments. If you do not qualify for the study, the CT results may not be used for this study but may be useful for other asthma research, if you agree. Please note that the CT scan is optional. This will be discussed in more detail below.

Chest x-ray: If tuberculosis cannot be ruled out on the basis of a blood test, the results from either a CT scan or a chest x-ray will be needed. If you choose not to have a CT scan, you will have a chest x-ray. A chest x-ray creates pictures of your lungs.

After all screening and baseline visits have been completed and study eligibility criteria are reviewed by the study doctor (site investigator), you will be informed about whether you qualify for continued participation in the study. If you qualify, you will begin treatment visits.

Treatment Visits

Treatment Periods: A treatment period is 16 weeks long followed by either 8 or 16 weeks of washout, during which you do not take the treatment.

On *MCT*, *Broncho-Vaxom and cavosonstat,* you will be required to have five monthly visits (during weeks 0, 4, 8, 12 and 16 beginning from the start of a treatment period). Visit 6 will occur during an 8-week washout.

On *clazakizumab,* you will be required to have five monthly visits (during weeks 0, 4, 8, 12 and 16 beginning from the start of a treatment period). This treatment requires a longer washout (16-weeks) and more visits than MCT, Broncho-Vaxom, cavosonstat and imatinib during the washout period due to increased length of the washout.

On *imatinib*, you will be required to have five monthly visits (during weeks 0, 4, 8, 12 and 16 beginning from the start of the treatment period). Visit 6 will occur during an 8-week washout. In addition to the labs performed at the monthly visits (see Table 3), safety labs will be collected during weeks 1, 2, 3, and 6 during the 16-week treatment period. Approximately 2 mL of blood will be taken for these labs during weeks 1, 3 and 6 and approximately 5 mL of blood will be taken for these labs during week 2.

The number of treatments you receive will depend upon when you enroll in the study and how many treatments you qualify for based on safety criteria. If you enroll at the beginning of the study you will be eligible for more treatments than participants who enroll at the end of the study.

Monthly treatment visits: Each treatment visit will take approximately 2-3 hours.

Treatment visits will include the following:

Peak Flow Meter and e-diary Compliance (all treatment visits): The study coordinator will review and discuss your compliance with the e-diaries and peak flow meters.
Controller Medication (all treatment visits): The study coordinator will review and discuss your compliance with your controller medication. You will receive more controller and rescue medication, if applicable.
Physical Exam (all treatment visits): You will receive a full physical exam during the first treatment visit and brief physical exams on the subsequent treatment visits.
Questionnaires (all treatment visits): You will be asked to update information about current medications and asthma symptoms and to provide us with information on any exacerbations that occurred between visits. You will also be asked about current medical conditions and any new symptoms.
Randomization (first treatment visit): During the first treatment visit of each treatment period you will be randomly assigned, based on your biomarkers, to one of these treatment groups or to the matching placebo:

clazakizumab, medium chain triglycerides (MCT), imatinib, Broncho-Vaxom or cavosonstat. You will not be able to choose which treatment group you are assigned to. Once randomized, the treatment group assignment cannot be changed. If you do not wish to participate in the study group to which you are randomized, you will not be able to participate in this study. You and the study staff will not know whether you are receiving active treatment or placebo. In case of an emergency, the study doctor will be able to find out whether you are re ceiving the active treatment or placebo.

Safety Labs - Blood and Urine (all treatment visits):

- Blood and urine will be collected *(as described above under Safety above)*
  - The total amount of blood we draw as you participate in the study during these visits will vary depending upon how long you stay in the study and how many treatments you qualify for before the study ends. Please see Table 3 at the end of this consent for the amount of blood we will take at each visit.
- Urine will be taken to assess pregnancy status on women who can become pregnant.

Biomarkers (first, third and fifth treatment visits): Biomarkers will be collected via blood, urine, breath analysis (for FeNO) and nasal swab. If your site requires COVID testing prior to the nasal swab collection, a nasal swab will not be collected on you.

Pulmonary Function Testing (first five treatment visits):

- *Medication withholds, as described above (first five treatment visits)*
- *Spirometry, as described above (first five treatment visits)*
- *Spirometry POST 4 puffs albuterol, as described above (first and fifth treatment visits)*

Dispense Study Treatment (first four treatment visits): You will receive study treatment. Treatment will come in either packets of powder, or will be administered subcutaneously (via an injection under the skin). Additional details of the drug administration are given in the treatment specific forms, below.

Storage and Future Use of Biospecimens

Biospecimens are collected in the PrecISE study during the run-in visit and the first, third and fifth treatment visits. It is important for you to understand how your biospecimens will be used and stored. The following describes what will happen to the biospecimens collected in this study.

For all of your biospecimens (urine, blood, nasal swabs, sputum), there is a high possibility that the genetic material (DNA, RNA, mitochondrial DNA, bacterial DNA, viral genetic material, etc.) will be useful for answering important research questions. Some of the experiments that might use this genetic material are not yet decided, but there will be interesting questions to answer in the future.

Blood: Blood will be shipped to the Cleveland Clinic Biorepository where it will be stored, with the following exception:

- Blood (equal to 1 tube) to isolate DNA from your blood cells (as described above) will first be sent to a PrecISE approved laboratory for genotyping. Any leftover genetic material (DNA) will be sent to the Cleveland Clinic Biorepository for storage so that it can be utilized later for further genetic testing in PrecISE.

Nasal swab: The nasal swab samples will be sent to the Cleveland Clinic Biorepository for storage and will be shipped periodically to the Mayo Clinic in Phoenix, Arizona for analysis. Any leftover specimens will be sent back to the Cleveland Clinic Biorepository for storage. This leftover sample may be utilized for other analyses in PrecISE, for example, genetic testing.

Urine: Urine will be shipped to the Cleveland Clinic Biorepository where it will be stored. Urine will be analyzed for a variety of proteins and other molecules, and may include analyses of genetic material.

Induced sputum: Sputum will be analyzed at the University of California, San Francisco (UCSF) Sputum Core as well as stored at the Cleveland Clinic Biorepository. The types of cells in the sputum will be analyzed using a portion of the sputum sample that is processed on a slide. These slides will be shipped directly to UCSF. The remainder of the sputum biospecimens will be either stored at the Cleveland Clinic Biorepository or temporarily stored at the Cleveland Clinic Biorepository until batch shipped periodically to the UCSF Sputum Core. For the samples sent to UCSF, the UCSF core will bank the sputum biospecimens and manage any future analyses of biomarkers in the sputum biospecimens. Analyses from your sputum will potentially include measures of gene expression by the sputum cells (or other genetic material, such as microbial DNA or RNA) and measures of multiple proteins and other molecules in the fluid from the sputum samples.

In addition to the biomarkers described above, other biomarkers will be measured at various times during the course of the study using a variety of different methods in a variety of different laboratories that specialize in these methods. To conduct these biomarker measurements, parts of samples already stored at the Biorepository will be sent in batches to the specialized laboratories. If any sample is left over after the required testing is finished, the samples at the specialized laboratories will either be destroyed or returned to the biorepository.

In some cases, instead of sending all samples to the Biorepository, local sites will keep extra specimens not needed for the study. If your local site is storing the extra specimens, you will be asked to sign a separate consent.

HOW MANY PEOPLE WILL PARTICIPATE?
Approximately 600 adults and adolescents (ages 12 years and older).

HOW LONG WILL I BE IN THIS STUDY?
The screening and run-in periods will last approximately eight to ten weeks. Each treatment period will last 16 weeks and the washout periods will last between 8-16 weeks, depending on the treatment. The length of time you are in the study will depend upon the number of treatments you receive, and the number of treatments you receive will depend upon when you enroll in the study. If you enroll early in the study, and qualify for each individual treatment, you could receive up to 5 treatments. The longest time you could be in the study is approximately 3 1/2 years and the shortest time is approximately 1 year.

SIDE EFFECTS AND RISKS THAT YOU CAN EXPECT IF YOU TAKE PART IN THIS STUDY
You may experience one or more of the risks indicated below from being in this study. In addition to these, there may be other unknown risks, or risks that we did not anticipate, associated with being in this study.

You will be informed of any findings of clear clinical significance that may be discovered during study procedures. There may be benefits to learning such results (such as early detection and treatment of a medical condition), but there are risks as well (such as problems with getting insurance or a job, or feeling worried about a finding for which no treatment is required or appropriate). If there is a finding of clear clinical significance, you can choose to have your physician alerted.

Please note that additional site specific risk language is included in Part 2 of the consent.

All Procedures
Rare: Breach of confidentiality.
Because this is a multi-site study and international in scope, data will be transmitted electronically. There is always the risk that a transmission could be intercepted and decoded. We will meet or exceed all standards of electronic security using only secure servers and encryption. We will protect your information, but there is a chance somebody might see it.

In-Person Questionnaires and Surveys
Likely: You may find the questions tiring, tedious, or embarrassing. You may choose not to answer a specific question or to decline a test at any time, however, there are some questionnaires that are required for study participation.

Blood Draw for Safety Labs, Genetic Research and Blood Biomarkers
Likely: The blood draw may cause bleeding, bruising, or pain. Some people become dizzy or feel faint.
Less Likely: None known.
Rare: Infection.
To minimize these risks, experienced medical personnel will perform the blood draws using aseptic (clean) technique.

Pulmonary Function Tests
Likely: None known.
Less Likely: Dizziness during the tests, coughing, feeling short of breath
Rare: The test may trigger severe breathing problems

Albuterol (for Pulmonary Function Tests)
Likely: Common risks associated with albuterol include headache, increased pulse rate, shakiness of hands, lightheadedness or dizziness.
Less Likely: None known.
Rare: Rare side effects to albuterol include low blood potassium, irregular heartbeat or heart rhythm, hyperactivity and an immediate increase in wheeze after dosing.

Medication Withholds
Withholding asthma medications can cause chest tightness and wheezing. Participants will be informed that if they cannot hold their medications and feel they need to take them, they should do so and call the study coordinator to let them know.
Likely: Chest tightness and wheezing, an increase in allergy or asthma symptoms may occur as a result.
Less Likely: None known.
Rare: None known.

Methacholine Challenge
Likely: Coughing, chest tightness, shortness of breath, and wheezing. You will be given albuterol for relief of symptoms. The symptoms are usually gone within a few minutes after using the albuterol medication for relief.
Less Likely: None known.
Rare: On rare occasion, severe bronchospasm can occur (this is when muscles that line the airways of the lungs constrict or tighten, reducing airflow).

Induced Sputum
Likely: Salty aftertaste, coughing, a feeling of needing to swallow.
Less Likely: Sore throat, shortness of breath, wheezing, chest tightness, lightheadedness, nausea or headache.
Rare: Severe asthma attack or a reaction to the salty water that you breathe in. Albuterol treatment will be available if this occurs.

Urine
There are no foreseeable risks to its collection.

Exhaled nitric oxide
There are no known risks to its collection.

CT Scan
Likely: During the CT scan, you will be exposed to a small amount of radiation (see Site Specific Consent, Part 2 for exact dose). The maximum amount of radiation you will be exposed to during the procedure is approximately equal to 20% of the annual allowed dose for a medical radiation worker. Although there are no proven harmful effects from this amount of radiation, long term effects on your health such as cancer cannot be ruled out. This dose estimate takes into account only the exposure to research procedures in this project. If you have participated in other research studies involving radiation exposure, you should be aware that the risk of effects of radiation exposure is thought to add up across all your exposures, including procedures performed as part of your medical care.
Less Likely: None known.
Rare: None known.

Chest X-Ray
Likely: During the chest X-ray, you will be exposed to a small amount of radiation (0.1 mSv), which is equal to the amount of radiation the average person is exposed to in 10 days from the environment.
Less Likely: None known.
Rare: None known.

EKG
Likely: None known.
Less Likely: Gel and patches that are applied to the skin may cause temporary redness and irritation. You may experience discomfort (pulling on the skin/hair) during removal of the sensors.

Rare: None known.

Nasal Swabs
Likely: There is a risk of mild discomfort and mild nasal stuffiness from the procedure.
Less Likely: None known.
Rare: A slight risk of nose bleeding.

Lung Diffusion Capacity Testing (DLCO)
Likely: None known.
Less Likely: You may feel short of breath during the exhalation part. If this occurs and does not go away on its own you may be given an albuterol treatment.
Rare: None known.

RISKS THAT ARE NOT KNOWN:
Because this treatment is investigational, meaning non-FDA approved, there may be risks that we do not know about at this time.

PREGNANCY/CHILDBEARING POTENTIAL
Because of the unknown risks of potential harm to an unborn baby from exposure to study medication and/or study procedures used in this study, you may not participate in this clinical trial if you are pregnant or plan to become pregnant during your study participation. Urine pregnancy tests will be conducted at all visits for all women of childbearing potential.

Some parts of this study might cause physical problems in an unborn baby. In addition, if you are or become pregnant, this study may involve risks to your embryo or fetus which are currently unforeseeable. You must tell the doctor immediately if there is any chance you are pregnant. If your partner is not sterilized by vasectomy, you must agree to use effective contraceptive measures from screening until 16 weeks after the last dose of study treatment. If you are currently breastfeeding, you may not participate in the study.

If you have a positive pregnancy test you will be unable to continue to participate in the study. You must agree to use effective contraception while you are in the study. Once you have completed all the study visits, there are no known effects from participating in this study that would cause increased risk to future pregnancies.

Additional follow-up information may be requested about the baby until at least one month after the birth of the baby, due to potential risk of abnormalities not present at birth. Information will be collected according to local and data privacy regulations.

For Female Patients
As mentioned above, we do not know if the study treatment has any effects on pregnancy, or an unborn or breastfed child. If you are a woman who can become pregnant, it is very important that you practice birth control to prevent pregnancy during this study. You must use a highly effective form of birth control from at least 1

month prior to screening through at least 16 weeks after receiving last dose of the study medication. How long after 16 weeks you continue to use the birth control should be discussed with the study doctor.

A highly effective method of birth control is defined as one that results in a low failure rate (i.e., less than 1% per year) when used consistently and correctly. Acceptable forms of highly effective birth control are listed below:

- Bilateral tubal ligation or bilateral tubal occlusion for females
- Male partner sterilization (vasectomy)
- Hormonal (pill, patch, ring, implant, injection, hormonal IUD)
- Copper IUD
- Male condom with either: a diaphragm (with spermicide) or cervical cap (with spermicide)*
- Abstinence
- Same-sex partner

*A male condom used in combination with a diaphragm (with spermicide) or cervical cap (with spermicide) is an acceptable form of birth control. Male condoms and female condoms used alone or in combination with each other are not acceptable methods of birth control, even if used with spermicide. Diaphragms and cervical caps with spermicide are also not acceptable when used without a male condom.

Your study doctor can discuss these options with you.

_____ By initialing here, I agree I am using one or more of the methods listed above and will continue to do so through the study OR I am not of child-bearing potential (premenarche, hysterectomy and/or bilateral salpingo oophorectomy or postmenopause).

For Male Patients

If you are a male who is sexually active with a female who can get pregnant, you must agree to use a medically acceptable form of birth control, such as barrier protection or sterilization (vasectomy), or you must agree that that your female partner will use one of the other methods listed below. You should inform your partner of the potential for harm to an unborn child. If your partner becomes pregnant while you are participating in the study, then you must notify the study doctor of your partner's pregnancy within 24 hours of receiving medical confirmation and she should promptly notify her doctor of your participation in this study. As per regulatory requirements, information will be collected about your partner's pregnancy until the outcome of the pregnancy is known.

Acceptable forms of highly effective birth control are listed below:

- Sterilization (vasectomy)
- Female partner has had bilateral tubal ligation or bilateral tubal occlusion
- Female partner takes hormonal birth control (pill, patch, ring, implant, injection, hormonal IUD)
- Female partner has copper IUD
- Male condom with either: a diaphragm (with spermicide) or cervical cap (with spermicide)
- Abstinence
- Same-sex partner

_____ By initialing here, I agree to use a medically acceptable form of birth control if I am sexually active with a female who can get pregnant OR I have had a vasectomy.

GOOD EFFECTS THAT MIGHT RESULT FROM THIS STUDY

There is no guaranteed benefit from participating in the study. There is a possibility that study treatments or information obtained while participating in this study could benefit you directly. It is hoped that information obtained from your participation will help us learn more about severe asthma and its treatments.

WHAT OTHER CHOICES DO I HAVE IF I DO NOT TAKE PART IN THIS STUDY?

Your other choices include getting standard treatment for your condition without being in a study. There may also be other studies in which you could participate. If you have any questions concerning alternative treatments, please see below. You and your doctor can decide on the best treatment for you.

OTHER TREATMENTS FOR SEVERE ASTHMA

Several treatments for severe asthma are available. These treatments have been shown to improve asthma control. You should be aware of these treatment options and discuss them with your asthma doctor, if you would like to learn more about them. If you decide to start on one of these drugs, you may still be a candidate for PrecISE in the future.

IS BEING IN THIS STUDY VOLUNTARY?

Taking part in this research study is completely voluntary. You may choose not to take part at all or stop participating at any time. If you decide not to be in this study, or if you stop participating at any time, you won't be penalized or lose any benefits for which you otherwise qualify.

CAN I STOP BEING IN THE STUDY?

Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. She or he will tell you how to stop your participation safely. Deciding not to be in the study or leaving the study before it is done will not affect your relationship with the researcher or your health care provider.
If you decide to withdraw from the study you may request that your data and stored samples not be used in any future research outside of PrecISE. If you wish to withdraw, we ask that you put this request in writing and send it to the site where you are participating. Please ask the site coordinator for more details.
A study coordinator will conduct an exit interview to ensure all appropriate steps have been taken to withdraw you from the study. You may decline to participate in the exit interview.

PARTICIPATION IN OTHER STUDIES

You **may not** participate in other studies where a drug or other treatment is given while you are enrolled in this study. Please inform the study coordinator if you are thinking about enrolling in another study.

CLINICAL TRIALS REGISTRY

A description of this clinical trial will be available on www.clinicaltrials.gov, as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

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HOW WILL PRIVACY AND PERSONAL INFORMATION BE PROTECTED?

Protecting your privacy is a top priority for PrecISE. Any information we obtain about you during this study will be treated as strictly confidential to the full extent permitted by applicable law.

Code numbers - not names: To ensure confidentiality, a code number will be assigned to you and your medical information. Files with your name and other identifying information will be electronically saved separately from your medical information on a secure computer that cannot be accessed by an unauthorized person. If your information is printed, it will be kept locked and accessible only to certified PrecISE personnel at the PrecISE clinical site. Only authorized PrecISE personnel will have access to your name and identifying information. PrecISE will not share sensitive information with you via text message nor publish identifiable information on Internet sites.

What is the risk of being identified? While we believe that the risks of being identified are very low and the benefits to science and the health of the community are large, there may be risks that we are not aware of at this time. In particular, we will share safety and quality control data with companies who are donating study drugs and equipment. While we will take all precautions to protect your privacy, there is a small risk of being identified.

The protected data developed for this project will not contain information that is used to identify you (such as your name, address, telephone number, or social security number), but it is possible that in the future people may develop ways to link your genetic or medical information back to you.

To protect you, the **Genetic Information Nondiscrimination Act (GINA)** is a federal law passed in 2008 that makes it illegal to discriminate on matters of employment and health insurance in the U.S. based on genetic information. If you were identified by your genetic information however, this could potentially be used in ways that may cause you or your family distress, such as revealing that you (or a blood relative) carry a genetic disease, or by leading to the denial of employment or insurance for you or a relative.

Publishing study results: When study results are published, your name and any other potentially identifying information will not be revealed. Results from this study and from your records may be reviewed and photocopied by the Office of Human Research Protection (OHRP) of the U.S Government or the Institutional Review Board of Vanderbilt University.

Who outside the study site may view or receive my information?

- U.S. Office for Human Research Protections
- The U.S. Food and Drug Administration (FDA)
- The study sponsor, National Heart, Lung, and Blood Institute
- PrecISE Data, Modeling, and Coordinating Center at the University of North Carolina – Chapel Hill, Chapel Hill, NC
- PrecISE Data and Safety Monitoring Board
- Other researchers within the PrecISE network
- Researchers within the Severe Asthma Research Program (SARP) Network, another severe asthma network sponsored by NHLBI (The SARP Network and the PrecISE Network have many of the same researchers, are sharing some study equipment and will have individuals who are participating in both studies. Data collected in PrecISE may be shared with SARP Network researchers.)
- Law enforcement or other agencies, when required by law

- Industry partners providing study interventions including: CSL Behring, Inc. located in the United States, Vitaflo International Ltd. located in Liverpool, England, Sun Pharmaceutical Industries located in Mumbai, India, OM Pharma, located in Meyrin, Switzerland, and Laurel Venture Capital Ltd located in Hangzhou, China
- Representatives from the Vanderbilt Human Research Protections Program (VHRPP), who manage the PrecISE IRB
- Other representatives of the University of North Carolina at Chapel Hill responsible for ethical, regulatory, or financial oversight of research
- Pharmaceutical Product Development (PPD), Highland Heights, KY (central laboratory for safety lab tests in the PrecISE study)
- LabCorp, Cincinnati, OH (patient service centers for additional safety lab tests in the PrecISE study)
- Qualtrics (survey software solution that participants may use to enter daily diary information)
- Collaborating researchers outside your site including researchers at:
    - University of California, San Francisco (UCSF) Sputum Core , San Francisco, CA (sputum laboratory for PrecISE)
    - Cleveland Clinic Biorepository , Cleveland, OH (biospecimen laboratory and biorepository for PrecISE)
    - Mayo Clinic, Phoenix, AZ (nasal swab laboratory for PrecISE)
    - The PrecISE Spirometry Overreading Core, University of Wisconsin-Madison, Madison, WI (assess quality of and grade breathing tests)
    - Advanced Pulmonary Physiomic Imaging Laboratory (APPIL), University of Iowa, Iowa City, IA (Radiology Reading Center for PrecISE)
    - VIDA Diagnostics Inc., Coralville, IA (Developer of the software used for CT image analysis)
    - Indiana University Genetic Testing Laboratories (IU GTL) (Genotyping Core for PrecISE)
- Companies or groups performing services for the research study, such as:
    - Pennington Biomedical (MCT food diary recall oversight and MCT assistance)
    - Medical International Research Inc. (MIR), in Waukesha, WI and Rome, Italy (maker of the home spirometer)
    - Vyaire Medical (maker of the clinic spirometer)
    - Propeller Health, Madison, WI (maker of the daily asthma symptom e-diary and sensors to measure controller medication use)
    - Other labs contracting with PrecISE for analysis of blood, urine, or biological specimens
    - Other people or organizations assisting with PrecISE research efforts (this may include drug manufacturers, distributors and/or their designees)
    - ZEPHYRx (maker of the app used to record results from the home spirometer)
    - Root Health (developer of an app used to help schedule and manage patient visits)
    - Trialfacts (clinical trial recruitment company that collects contact information and responses to screening questions from potential participants.

It is possible that your spirometry data from previous studies may be used to qualify you for PrecISE. If it is necessary to obtain these data, they will be sent, via secure transfer, to the PrecISE Spirometry Overreading Core at the University of Wisconsin-Madison for review.

With the approval of the PrecISE investigators, your samples may be shared with PrecISE and SARP investigators for research in asthma and related diseases. SARP is the "Severe Asthma Research Program" sponsored by the NIH to understand the mechanisms of severe asthma. Many of the investigators in PrecISE are part of SARP.

WILL ANY RESEARCH-RELATED PROCEDURES BE BILLED TO ME?

No. The sponsor has agreed to pay for all procedures associated with this research study; you or your insurer will not be billed. However, results from hospital procedures done during the research visit (such as the CT scan) may result in a need for additional testing. In the event additional testing is required, the study will not pay for these tests or procedures. As mentioned above, the study will provide the Advair Diskus as controller medication and albuterol sulfate as rescue medication. If you decide to use your own controller or rescue medication, you will need to pay for this.

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STUDY QUESTIONS – *PLEASE COMPLETE ALL QUESTIONS BELOW. You may choose to answer 'No' to the following questions without jeopardizing your participation in the study.*

Text Messages
In order to participate in the study, I understand I must have or get a device such as an iPhone, iPad or iPod, or a smartphone or tablet. I understand that I may receive text messages from Qualtrics twice a day in order to complete an e-diary survey.

_____
Participant's Initials

Consent to share findings with personal doctor
I agree that PrecISE may share findings important to my health from PrecISE tests and examinations with my personal doctor.

Circle one: Yes No _____
Participant's Initials

Consent to be contacted about other studies
I agree to allow PrecISE staff and investigators to contact me about participating in additional assessments and procedures relating to the PrecISE study. I understand that I am not required to participate in these if contacted and that it will have no effect on my participation in the main PrecISE study.

Circle one: Yes No _____
Participant's Initials

Study supplied Controller and Rescue Medication
I agree to receive the optional, study supplied, controller medication (Advair Diskus).

Circle one: Yes No _____
Participant's Initials

I agree to receive the optional, study supplied, rescue medication (Ventolin).

Circle one: Yes No _____
Participant's Initials

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CT SCAN

The CT scan is a special type of x-ray examination that will be done during the Run-in visit, if you agree. You will be asked to lie on a table with your arms resting above your head. You will need to remain still and hold your breath for about 10-20 seconds during each scan. You will then be asked to breathe out and hold your breath again and the scan will be repeated. If you are a woman who can become pregnant, you will have a pregnancy test to make sure that you are not pregnant before having the CT scan.

The reason for the CT scan is to look for signs of tuberculosis and also to measure your airway structure. We will work with a group that is experienced in collecting and reading the scans at the University of Iowa to ensure the scans are collected properly. The images from the CT scans will be stored at the site where it was collected and then will be sent, electronically, to the University of Iowa using software that will remove identifying information and assure proper procedures are being followed.

During the CT scan, you will be exposed to a small amount of radiation (see Site Specific Consent, Part 2, for exact dose). The maximum amount of radiation you will be exposed to during the procedure is approximately equal to 20% of the annual allowed dose for a medical radiation worker. Although there are no proven harmful effects from this amount of radiation, long term effects on your health such as cancer cannot be ruled out. This dose estimate takes into account only the exposure to research procedures in this project. If you have participated in other research studies involving radiation exposure, you should be aware that the risk of effects of radiation exposure is thought to add up across all your exposures, including procedures performed as part of your medical care.

Due to scheduling constraints, the CT scan may be conducted before you have completed all of the study's eligibility assessments. If you do not qualify for the study, the CT results may not be used for this study but may be useful for other asthma research, if you agree.
You may choose to answer 'No' to the following question without jeopardizing your participation in the study.

Please indicate your response below:

I agree to have a CT scan performed.

Circle one: Yes No

_____
Participant's Initials

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CONSENT TO ADDITIONAL SHARING OF YOUR SAMPLES AND INFORMATION OUTSIDE OF PRECISE AND THE SEVERE ASTHMA RESEARCH PROGRAM

In addition to research questions concerning asthma and related diseases other research questions may arise. If you are willing to share them, your tissues, health information, and genetic material collected in PrecISE will be shared with other researchers to help answer such questions. Please note that you would not benefit financially from sharing of these data and materials. Your willingness to share data and materials with other researchers or for other studies will not jeopardize your participation in PrecISE.

You may choose to answer 'No' to the following question without jeopardizing your participation in the study.

Please indicate your response below:

I give consent for my tissue samples (for example, urine, blood, nasal swabs and/or sputum), health information (for example, biomarkers and questionnaires), and genetic data and material that are collected as part of the PrecISE study to be shared with other researchers for other research questions.

Circle one: **Yes** **No**

_____
Participant's Initials

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DEPOSITION OF DATA AND BIOSPECIMENS IN PUBLIC REPOSITORIES

As mentioned above, blood, nasal swabs, urine, and induced sputum will be collected and stored for analysis of biomarkers in the PrecISE study. This storage will occur at the Cleveland Clinic Biorepository and at the UCSF Sputum Core. Periodically, throughout the PrecISE study, new biomarkers will be measured from these stored samples. The results of these tests will help PrecISE investigators determine how well a treatment worked or to determine if biomarkers other than the ones that have already been measured would have been useful to determine a treatment response. At the end of the study, there is a high likelihood that we will not have utilized all of your biospecimens and that we will still have some of your samples frozen. With your permission, we would like to make these extra samples available for future use in other studies, by deposition in the Biorepository for the National Heart Lung Blood Institute (NHLBI) (called BioLINCC).Samples stored in BioLINCC will be made available to qualified researchers studying other diseases. In order to make these samples useful for research, we will also need to store your associated clinical study data (for example, the treatment you are on, your age and gender, your answers to the questionnaires, your lung function results, your asthma symptoms, etc.). Your samples and your clinical data will be used for future analyses only if you agree. The samples will be de-identified (not list your name). The future use of your samples and information may contribute to learning more about disease or help to study the genetics related to a specific condition.

The results of tests performed on stored samples or reports resulting from the analysis of your samples will not be given to you or your doctor and they will not be put in your medical record. They will not identify you and will not affect your routine medical care.

There is no benefit to you from the storage of samples and information. However, the use of your samples and information may help researchers learn more about your disease. The purpose of storage and sharing data is to make information available for use in health research and to share what is stored with other researchers. Collecting, storing, sharing information and making it available for other studies may help people in the future. Coded information put into databases together with other stored information from many studies conducted in different places allow researchers to study the combined information and learn even more about health and many different diseases.

There may be unknown risks associated with the storage of samples and information. For example, if the future research involves genetic testing, it is possible that it could be traced back to you because your genes are specific to you. We will make every attempt to protect your confidentiality and to make sure that your personal identity does not become known.

You can change your mind at any time until the end of the study and ask that your samples not be used for future studies. This request should be made in writing to the study doctor. If you make this request, all samples remaining at the end of the study will be destroyed. Your decision regarding the use of samples in future studies will not affect your ability to participate in this study.

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You may choose to answer 'No' to the following question without jeopardizing your participation in the study.

Please indicate your response below:

If all of my samples are not used by the end of the PrecISE trial, I agree - to the extent they are not retained by the PrecISE investigators - to the future storage and sharing of my de-identified tissue samples (for example, urine, blood, nasal swabs and/or sputum), health information (for example, biomarkers and questionnaires), and genetic data and material for use in future studies as described above.

Circle one: **Yes** **No**

_____
Participant's Initials

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NEW TREATMENTS
This study involves multiple potential treatments. Detailed information about these treatments is included below. If new treatments are added to the study later on, you will be asked to review information about the new treatments and consent to those separately. **If you choose not to consent to the new treatments when they are added to the study, your participation with the current treatments will not be affected.**

Please indicate your response below:

NEW PARTICIPANTS ONLY
I agree to all treatments currently approved for PrecISE (medium chain triglycerides (MCT), clazakizumab, imatinib, Broncho-Vaxom and cavosonstat).

Circle one: **Yes** **No** _____ **Participant's Initials**

ADOLESCENTS TURNING 18
I agree to receive all treatments for which I have not yet given consent. This may include clazakizumab, imatinib, Broncho-Vaxom and/or cavosonstat. I understand that if I do not agree to receive the newly added treatment(s), then I will continue the study and can be randomized to any of the treatments in the set of treatments that I already agreed to.

Circle one: **Yes** **No** _____ **Participant's Initials**

OTHER CURRENT PARTICIPANTS ONLY WHO HAVE NOT REFUSED ANY INTERVENTIONS
I agree to receive all treatments for which I have not yet given consent. This may include imatinib, Broncho-Vaxom and/or cavosonstat. I understand that if I do not agree to receive the newly added treatment(s), then I will continue the study and can be randomized to any of the treatments in the set of treatments that I already agreed to.

Circle one: **Yes** **No** _____ **Participant's Initials**

OTHER CURRENT PARTICIPANTS WHO HAVE REFUSED ONE OR MORE INTERVENTIONS
Participants who have refused one or more interventions may not receive any additional interventions.

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Schedule of Events***								
Study Visit:	**Screening**	**Run-in**	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**
	1-2 Visits		**Can occur multiple times**					
Timing: (week number)	-8 to -10	-4	0	4	8	12	16	20
What happens /What you need to do:								
Your study doctor or coordinator will check that you are suitable to take part in the study	X	X						
Your study doctor or coordinator will perform a physical exam	X	X	X	X	X	X	X	X
Your study doctor or coordinator will dispense more controller medication to you, if you choose to receive it	X	X	X	X	X	X	X	X
You will review your peak flow meter, sensors for your controller medication and rescue inhaler and e-diary data	X	X	X	X	X	X	X	X
You will be randomized to a treatment or placebo			X					
You will get study drug			X	X	X	X		
You will fill out surveys on your medical, asthma and allergy history****	X							
You will fill out surveys about how you are feeling, and about any other medicines you are taking****	X	X	X	X	X	X	X	X
You will fill out surveys about your household****	X							
You will go through Pulmonary Function Testing**	X	X	X	X	X	X	X	X
Blood and Urine will be taken for Safety Tests*****	X	X	X	X	X	X	X	X
Biospecimens (blood, urine, and nasal swab) will be collected to determine your biomarkers and to assess your progress; FeNO will be measured. *******		X	X	X	X	X	X	X
You will be asked to have an CT scan		X						
You will be asked to produce a sputum sample		X						
An EKG will be performed******		X						
An x-ray will be performed, if necessary		X						

***Please note that participants on clazakizumab will have more than one visit during the Washout phase at the end of the treatment.**
****Pulmonary function tests may be conducted in the home in addition to in the clinic at the Screening, Run-In, V1 and V6 visits.**
***** Please note that it is possible that some procedures could be performed at time points that are different than what is noted in the table.**
******These could be done in-person or remotely.**
*******Safety tests will either be conducted in clinic or at patient services centers (ex. LabCorp)**
********EKGs are not required for every intervention**
*********If your site requires COVID testing prior to the nasal swab collection, a nasal swab will not be collected on you.**

Table 3. Blood Volume Draws Per Visit

	Safety	Biospecimen	Total
Run-In Visit	21 ml = 4.3 tsp	2.5 ml = .5 tsp	23.5 ml = 4.8 tsp
Treatment Visit 1	6 ml = 1.2 tsp	50 ml = 10 tsp	56 ml = 11.2 tsp
Treatment Visit 2	6 ml =1.2 tsp	20 ml = 4 tsp	26 ml = 5.2 tsp
Treatment Visit 3	6ml = 1.2 tsp	20 ml = 4 tsp	26 ml = 5.2 tsp
Treatment Visit 4	6 ml = 1.2 tsp	20 ml = 4 tsp	26 ml = 5.2 tsp
Treatment Visit 5	6 ml = 1.2 tsp	50 ml =10 tsp	56 ml = 11.2 tsp
Wash-out	6 ml = 1.2 tsp	--	6 ml = 1.2 tsp
TOTAL	57 ml = 11.5 tsp	162.5 ml = 33 tsp	219.5 ml = 44.5 tsp

*** Additional volume may be required if a test fails or if there is a safety lab that needs to be repeated. For participants randomized to imatinib (or matching placebo), additional monitoring labs will be performed in weeks 1, 2, 3, and 6 (described above in "Treatment Visits" section).**

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TREATMENT INFORMATION DOCUMENT - CLAZAKIZUMAB

Information about the treatment:
Interleukin-6 (IL-6) is a chemical in the body called a "cytokine". It is a messenger that the body uses to send signals about inflammation in various parts of the body. Sometimes the levels of IL-6 in the body are high, particularly with certain types of inflammation that may occur outside of the lungs. These levels may be high particularly in patients who are older or who are obese. It is possible that in these situations, the high IL-6 in the body may lead to poor asthma control. Targeting IL-6 with medication (Anti-IL6 drugs) has been shown to be useful in chronic inflammatory diseases such as rheumatoid arthritis, giant cell arteritis, and cardiovascular disease.

How will the treatment be administered?
Clazakizumab, an anti-IL6 drug (also referred to as a "biologic"), will be administered subcutaneously (via an injection under the skin) by a doctor or a nurse, at a dose of 12.5 mg. You will receive a total of 4 injections, one every 4 weeks. The dose may be decreased to 6.25 mg (one-half of the standard dose) if during treatment blood tests demonstrate mild injury to the liver or bone marrow (the part of the body that makes immune cells). If you have a dose adjustment to the lower 6.25mg, you will remain at the 6.25 dose until the end of the treatment unless you meet criteria for discontinuation of the drug. If you meet criteria for discontinuation of the drug you will not be given additional drug doses, but you will remain in the trial and complete all procedures.

Are there treatment specific procedures?
During the run-in and treatment visits there will be blood taken for additional safety tests.

What are the risks of this treatment?
Risks include:
Likely: None known.
Less Likely: Infections, injection site reactions, neutropenia (low levels of blood cells that fight infection), elevated liver enzymes, hepatotoxicity (injury to the liver), and immunosuppression.
Rare: Risk of tuberculosis and opportunistic infections, serious infections, gastrointestinal perforation, thrombocytopenia (low blood platelet count. Platelets (thrombocytes) help blood clot. Platelets stop bleeding by clumping and forming plugs in blood vessel injuries), elevated lipids.

Clazakizumab may increase the liver's metabolism of certain drugs and because of this may decrease the effectiveness of some drugs, including birth control medications. Participants should discuss their contraception strategy with a healthcare provider. In addition, clazakizumab decreases immune response and because of this may decrease the effectiveness of vaccines. Vaccines work by producing an immune response to viruses and bacteria. If you get a vaccine shot while you are taking clazakizumab or in the 5 month period after you stop taking clazakizumab, then it is possible that clazakizumab may weaken the effect of the vaccine. For this reason, it is recommended that you receive all vaccines your doctor recommends for you (based on your age and your specific medical history) before you start clazakizumab treatment. And in relation to Covid-19 vaccine, you will need to have completed the vaccine regimen to be eligible for randomization to clazakizumab (active or placebo) unless you are unable to receive a Covid-19 vaccine for medical reasons or you choose to opt out of vaccination for other reasons.

What are possible benefits?
Medications similar to clazakizumab have been shown to improve symptoms in patients with other inflammatory diseases such as Rheumatoid Arthritis, Giant Cell Arteritis, Psoriatic Arthritis, and Polyarticular Juvenile Idiopathic Arthritis, and Castleman's Disease. It is possible that this medication will also improve symptoms in asthma, improve lung function, and decrease asthma exacerbation rates.

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TREATMENT INFORMATION DOCUMENT - MEDIUM CHAIN TRIGLYCERIDES (MCT)

Information about the treatment:
Medium chain triglycerides (MCT) is a food supplement thought to improve asthma control via a potential link between metabolism, obesity, and asthma.

How will the treatment be administered?
The treatment will come in packets of powder that can be mixed in a variety of foods and beverages. It is ideal to have at least a 2 hour interval between each consumption of the supplement. It is best to take the supplement before or with meals. Participants will be assigned a dose based on the number of calories required to maintain their bodyweight. This will be about 15% of total daily calories and most participants will be assigned between 3-4 packets/day. Participants will gradually increase the number of packets consumed each day over the course of the first 2 weeks.

Are there treatment specific procedures?
During treatment visits, participants will report foods they have eaten, complete a GI side-effects questionnaire, and give urine and blood to monitor safety specific to the MCT intervention.

What are the risks of this treatment?
MCT are well tolerated by most people.
Risks include:
Likely: Stomach discomfort
Less Likely: Gastrointestinal discomfort including diarrhea, vomiting, irritability, nausea and intestinal gas
Rare: Urgent need to pass a bowel movement, severe short-term diarrhea and dehydration

What are possible benefits?
Studies suggest benefits of MCT for cardiovascular disease. MCT may increase the feeling of fullness and decrease in the amount of food eaten. A potential benefit may include a reduction in weight and waist size.

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TREATMENT INFORMATION DOCUMENT - IMATINIB

Information about the treatment:
Mast cells are cells that live in tissues in your body. They are responsible for producing substances that cause your airways to narrow, swell, and produce mucus. All these things happen when you have asthma. Imatinib is a drug that blocks activation of these cells. In early, small studies in severe asthma it has been shown to reduce airway narrowing and decrease the "twitchiness" of asthmatic lungs. We would like to fully understand the effectiveness of imatinib in severe asthma and see if we can identify patients who might be more likely to respond to it.

How will the drug be administered?
You will take imatinib by mouth. At first you will take 200 milligrams which is 2 pills a day and after two weeks you will take 4 pills a day. You take all the pills at once with water.

Are there any treatment specific procedures?
Some patients who are treated with imatinib develop low blood phosphate levels and will need to take phosphate pills. We will monitor your blood tests and give you phosphate if necessary whether you are taking imatinib or placebo. If you are taking placebo, you may be given placebo phosphate.

Foods and drugs you will need to avoid:

1. The use of grapefruit juice should be avoided.
2. Ibuprofen (Advil or Motrin) should be avoided. Other pain relievers such as naproxen (Aleve), aspirin, and others can be used.

Imatinib should be taken with a meal and a large glass (8 oz./200 ml) of water.

What are the risks of treatment?
What we know about the risks of treatment with imatinib comes from animal studies and studies in people, with the majority of those patients having cancer. It is unclear whether the risks noted in studies of patients actually relate to side effects from imatinib and not to the cancers themselves that these patients had.

After studying more than 10,000 patients treated with imatinib, less than one in ten patients had severe side effects, and the majority of those resolved when imatinib therapy was stopped.

Most risks related to imatinib are mild and usually appear during the first month of therapy.

Risks associated with imatinib:

Likely (*more than 1 in 10 patients*): swelling due to fluid retention (mild edema), headache, nausea, vomiting, diarrhea, low red blood cell count (anemia), swelling around the eyes (periorbital edema), skin rash, upset stomach (indigestion), pain in muscles and bones, low blood phosphate levels (hypophosphatemia, corrected with monitoring and supplementation), muscle cramps

Less likely (*between 1 in 100 and 1 in 10 patients*): loss of appetite, dizziness, difficulty sleeping, passing gas (flatulence), constipation, liver problems, itching, fatigue (tiredness), blurred vision, mouth ulceration (ulcer, canker), bleeding and clotting disorders (hemorrhage, thrombocytopenia), anxiety, chills, depression, fever, upper

airway tract infection, lung infection (pneumonia), flu-like symptoms, taste disturbance, difficulty breathing (dyspnea), abdominal pain, abdominal distension, acid reflux (gastroesophageal reflux disease), dry mouth, swelling of the lining of the stomach (gastritis), dry skin, skin redness, hair loss, sweating, night sweats, skin sensitivity to light, joint swelling, weight gain, blood electrolyte abnormalities (low blood potassium levels), low blood protein levels (hypoproteinemia and hypoalbuminemia), coughing, nosebleeds, flushing, dry eyes, swelling of the eyelid lining (conjunctivitis), bleeding underneath the eyelids, shedding of tears (lacrimation), reduced sense of touch or sensation, skin tingling or numbness; decrease in red blood cells, white blood cells, and platelets; bleeding in the stomach or intestines, and decrease in kidney function

Rare (*less than 1 in 100 patients*): liver damage (hepatotoxicity), inability of the heart to circulate blood well (congestive heart failure), high blood pressure in circulation of the lungs (pulmonary hypertension), bleeding in the brain and spinal cord (central nervous system hemorrhage; seen in patients with cancer and could be related to cancer itself and not imatinib). Motor vehicle accidents have been reported in patients with cancer taking imatinib. Most of these are not suspected to be caused by imatinib, but dizziness, blurred vision, and sleepiness have been reported. Thirty patients with asthma who received imatinib did not report these symptoms. You should take caution while driving or operating heavy machinery.

Allergic Reactions: With any drug, an allergic reaction can occur. Allergic reactions can be mild or more serious, and can even result in death. Common symptoms of an allergic reaction are rash, itching, skin problems, swelling of the face and throat, or trouble breathing. Imatinib is not known to commonly cause allergic reactions. If you think you are having an allergic reaction, call the study doctor right away. If you are having trouble breathing, call 911 immediately.

Imatinib may decrease certain types of immune responses and because of this may decrease the effectiveness of vaccines. Vaccines work by producing an immune response to viruses and bacteria. If you get a vaccine shot while you are taking imatinib or in the 12 day period after you stop taking imatinib, then it is possible that imatinib may weaken the effect of the vaccine. For this reason, it is recommended that you receive all vaccines your doctor recommends for you (based on your age and your specific medical history) before you start imatinib treatment. In specific, in relation to the Covid-19 vaccine, you will need to have completed the vaccine regimen to be eligible for randomization to imatinib (active or placebo) unless you are unable to receive a Covid-19 vaccine for medical reasons or you choose to opt out of vaccination for other reasons.

Risks to an Embryo or Fetus, or to a Breastfeeding Infant: Animal studies suggest that imatinib might cause abortion and cause harm to a fetus or embryo (developing baby still in the womb) when it is taken in very high doses (above the levels used in our study). Because of these risks, women cannot take part in this study if they are:

- Pregnant
- Trying to become pregnant
- Breastfeeding

If you are sexually active and able to become pregnant, you and/or your partner must agree to use two of the birth control methods listed in this document. You must use birth control while receiving imatinib as well as 12 weeks after stopping imatinib. If you become pregnant during the treatment period, we will ask you to stop participating in the PrecISE study and we would like to contact you until your delivery to make sure you and your baby do not have any complications.

Imatinib doses may be reduced.
If any of the side effects listed in this consent form occur, the study doctor will either reduce the dose or stop the study drug and have you come in for additional blood draws. The side effects should resolve. Additionally, the study medical monitor is monitoring some of your labs (all CBC results except hematocrit, ALT, AST, bilirubin, eGFR and phosphorus) to determine if they remain normal. If there is a safety concern the medical monitor will immediately contact your study team to discuss the safety lab results. The study team will have access to these lab results and can share these results with you.

Because imatinib may cause abnormalities in phosphate levels, phosphorus is being measured to determine if a phosphate supplement should be started.

If you are taking a placebo, you may be instructed to reduce your dose, come in for additional blood tests or take a placebo instead of phosphate. These sham procedures are meant to keep you and the study team from knowing whether you are on active or placebo treatment.

What are the possible benefits of treatment?
It is possible that imatinib may improve your lung function, decrease your asthma symptoms, and possibly decrease exacerbations. We do not yet know for sure if this is the case.

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TREATMENT INFORMATION DOCUMENT - BRONCHO-VAXOM

Information about the treatment:
Broncho-Vaxom is an oral medication thought to improve asthma control by the reduction of asthma exacerbations and respiratory infections in affected patients. Broncho-Vaxom has been shown to potentially modify the gut microbiome, which leads to regulating airway inflammation in animal models of asthma.

How will the treatment be administered?
The treatment will come in capsules and should be consumed in the morning on an empty stomach. The capsules (2 x 3.5mg once daily) can be swallowed with water or the contents mixed with beverages. Participants will consume the Broncho-Vaxom capsules daily for the 4-month treatment period.

Are there treatment specific procedures?
During treatment visits, participants will perform the study-related procedures and provide stool samples to monitor biological markers.

What are the risks of this treatment?
Broncho-Vaxom is well tolerated by most people.
Risks include:
Possible: Diarrhea or headache
Less Likely: Abdominal pain, nausea, vomiting, a skin rash accompanying a disease or fever, hives, difficult or labored breathing, cough, asthma, and tiredness.
Rare: Fever and allergic reactions.

What are possible benefits?
Broncho-Vaxom studies have shown to improve symptoms in adult patients with chronic obstructive pulmonary disease (COPD). Oral powder of the bacteria have been shown to prevent moderate and severe asthma exacerbations in children aged 6-16 years.

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TREATMENT INFORMATION DOCUMENT - CAVOSONSTAT

Information about the treatment:
Cavosonstat is a medicine that blocks an enzyme that is believed to cause the airway to narrow in many patients with asthma.

How will the treatment be administered?
The treatment will come in a bottle of capsules and will be taken by mouth twice per day.

Are there treatment specific procedures?
During treatment visits, participants will be asked to collect exahlaed breath condensate to measure whether the medicine is working effectively in the lungs. This will take approximately 7 minutes to complete per test.

What are the risks of this treatment?
In all studies to date, cavosonstat is tolerated well.
Risks Include:
Likely: None
Less Likely: Weight gain was observed in cystic fibrosis patients, but this is believed to be a cystic fibrosis-specific effect.
Rare: None known.

What are possible benefits?
Studies suggest benefits of cavosonstat to reduce airway inflammation and promote relaxation of airway smooth muscle in patients with increased levels of the target enzyme in their lungs.

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CONTROLLER MEDICATION INFORMATION DOCUMENT – ADVAIR DISKUS

Information about the medication:
A controller medication is a long-term maintenance medicine that works over a period of time to ease airway inflammation and help prevent asthma symptoms.

How will the drug be administered?
It will be administered via an inhaler.

What are possible side effects of Advair Diskus?

- upper respiratory tract infections
- headaches
- dizziness
- nausea
- vomiting
- stomach upset
- diarrhea
- yeast infections of the mouth or throat (oral thrush)
- sore throat
- dry mouth/nose/throat
- stuffy nose
- sinus pain
- cough
- sore throat
- hoarseness or deepened voice
- musculoskeletal pain

What Drugs, Substances, or Supplements Interact with Advair Diskus?
Advair Diskus may interact with amiodarone, diuretics (water pills), HIV medicines, MAO inhibitors, antidepressants, antibiotics, antifungal medications, or beta-blockers. Tell your doctor all medications and supplements you use.

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RESCUE MEDICATION INFORMATION DOCUMENT – VENTOLIN HFA

Information about the medication:
A rescue medicine is a fast-acting medicine that works immediately to relieve asthma symptoms when they happen.

How will the drug be administered?
It will be administered via an inhaler.

What are possible side effects of Ventolin HFA?

- worsening trouble breathing, coughing, and wheezing (paradoxical bronchospasm). If this happens, stop using Ventolin HFA and call your healthcare provider or get emergency help right away. This is more likely to happen with your first use of a new canister of medicine
- heart problems, including faster heart rate and higher blood pressure
- possible death in people with asthma who use too much Ventolin HFA
- serious allergic reactions. Call your healthcare provider or get emergency medical care if you get any of the following symptoms of a serious allergic reaction:
  - rash
  - hives
  - swelling of your face, mouth, and tongue
  - breathing problems
  - changes in laboratory blood values (sugar, potassium).
- Common side effects of Ventolin HFA include:
  - sore throat
  - upper respiratory tract infection, including viral infection
  - cough
  - muscle pain
  - your heart feels like it is pounding or racing (palpitations)
  - chest pain
  - fast heart rate
  - shakiness
  - nervousness
  - dizziness

Get medical help right away if Ventolin HFA no longer helps your symptoms (like wheezing and trouble breathing), if your symptoms get worse, or if you need to use your inhaler more often.

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Version: **3.0**

Part 2 of 2: STUDY SITE INFORMATION

Site Name:	University of Wisconsin-Madison
Site Principal Investigator:	Loren Denlinger, MD, PhD
Site Principal Investigator Contact:	608-261-1552
Site Study Coordinator Contact:	608-263-0524 pulm-research@medicine.wisc.edu

This part of the consent form includes information about the site that is asking you to participate in this study and is specific to participation at your site only. Before making your decision, both the site-specific information and the general study information should be reviewed with you.

SITE-SPECIFIC PROCEDURES AND RISKS

CT Scan

During the CT scan, you will be exposed to a small amount of radiation (3-9mSv). Please see the CT Scan section in **Part 1 of 2** for more information about what this means.

COSTS TO YOU IF YOU TAKE PART IN THIS STUDY

There is no cost to you for taking part in this study.

PAYMENTS FOR YOUR TIME SPENT TAKING PART IN THIS STUDY OR EXPENSES

You will receive payments to help cover the costs of your participation in PrecISE. The amount you receive depends on which parts of the study you complete. We will pay you the amounts listed in the tables on the next page. If you complete all procedures in a visit, you will receive the full amount listed. If you only complete some of the procedures in a visit, you will be paid for the portion of the visit you completed. Payment will be provided at the end of each visit. If you choose to leave or we take you off study for any reason, you will receive payment for the visits you completed.

The payment schedule is described on the following page.

For the Screening and Run-in visits:

Visit Description	Approximate Length	Reimbursement	Compliance Bonus
Screening Visit A	5.0 hrs	$125	
Screening Visit B (only if needed)	2.0 hrs	$75	
Screening Visit C (only if needed)	0.5 hrs	$25	
Run-in	4.0 hrs	$100	+ up to $50

For each Treatment Period:

Visit Description	Approximate Length	Reimbursement	Compliance Bonus
Treatment Visit 1	4.0 hrs	$75	+ up to $50
Treatment Visit 2	3.0 hrs	$75	+ up to $50
Treatment Visit 3	3.0 hrs	$75	+ up to $50
Treatment Visit 4	3.0 hrs	$75	+ up to $50
Treatment Visit 5	3.0 hrs	$75	+ up to $50
Washout Visit 5a (for Clazakizumab arm only)	2.0 hrs	$50	+ up to $50
Washout Visit 5b (for Clazakizumab arm only)	2.0 hrs	$50	+ up to $50
Washout Visit 6	1.0 hrs	$200	+ up to $50

Additionally, for the Run-in visit and Treatment visits you will be paid up to $50/visit extra depending on how often you complete your daily study tasks (e-diary and peak flows, and take your study medications). If you complete your daily study tasks at least 80% of the time, you will earn the full $50/visit, if you complete your daily study tasks between 50%-79% of the time, you will earn $25/visit. There is no compliance bonus if you completed your daily study tasks less than 50% of the time.

There may be additional times we ask you to meet with the study team. Some examples may include safety visits if your asthma worsens, additional safety labs required for a treatment arm, repeat blood draw for abnormal labs, remote spirometry prior to an in-person study visit, or to get a COVID-19 test prior to a study procedure. You will be paid $20 for each extra visit.

If you live outside the greater Madison area (further than 20 miles from UW Hospital), you will also be reimbursed for mileage.

Additional non-monetary compensation
If you do not own a device that meets the requirements for this study, we can lend you a device for the duration of the study. The cost of the device will be deducted from your initial study payment. Upon completion of your participation in the study we will ask you to return the device we lent to you. If you

return the device to us within 4 weeks after you finish the study, we will give you back the money deducted from your initial payment. You will be responsible for paying for the costs of your service plan, if you choose to use one.

Do you wish to borrow a device for the duration of the study? Please initial by your choice:
_____ Yes _____ No

You will be provided with free parking or other transportation arrangements as needed for each in-person study visit. In addition, for study visits that take longer than 4 hours, you may receive a meal voucher for the UWHC cafeteria or be provided with small snacks. Nonmonetary incentives such as tote bags, water bottles, or other small gifts may be given at certain study visits.

PAYMENT IN CASE YOU ARE INJURED BECAUSE OF THIS RESEARCH STUDY

If you are injured or get sick because of this study, medical care is available to you through UW Health, your local provider, or emergency services, as it is to all sick or injured people.

- If it is an emergency, call 911 right away or go to the emergency room.
- For non-emergency medical problems, contact the study team for instructions.
- Call the Lead Researcher, Dr. Loren Denlinger, at 608-263-0524 to report your sickness or injury.

Here are some things you need to know if you get sick or are injured because of this research:

- If the sickness or injury requires medical care, the costs for the care will be billed to you or your insurance, just like any other medical costs.
- Your health insurance company may or may not pay for this care.
- No other compensation (such as lost wages or damages) is usually available.
- UW-Madison and UW Health do not have a program to pay you if you get sick or are injured because of this study.

By signing this consent form and taking part in this study, you are not giving up any legal rights you may have. You keep your legal rights to seek payment for care required because of a sickness or injury resulting from this study.

WHAT IF I HAVE QUESTIONS?

If you have questions about this research, please contact the Lead Researcher, Dr. Loren Denlinger, at (608) 261-1552. If you have any questions about your rights as a research subject or have complaints about the research study or study team, contact UW Health Patient Relations at (608) 263-8009. The Patient Relations Representatives work with research subjects to address concerns about research participation and assist in resolving problems.

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For additional information about giving consent or your rights as a person in this study, to discuss problems, concerns, and questions, or to offer input, please feel free to call the Vanderbilt University Medical Center Institutional Review Board Office at (615) 322-2918 or toll free at (866) 224-8273.

WILL I RECEIVE THE RESULTS OF RESEARCH TESTS?

Communicable Diseases

This study requires testing that may show you have human immunodeficiency virus (HIV), hepatitis B, hepatitis C, or tuberculosis (latent or active). If the tests indicates you have HIV, Hepatitis B, Hepatitis C, or tuberculosis, we will inform you of the results of the test by phone within one week. The results will also be placed in your medical record and reported to state or federal health officials as required by law. We can provide you with a list of resources to assist you in understanding the results.

If you test positive for human immunodeficiency virus (HIV), the Wisconsin health department will be informed of the results. The health department may contact you to help with counseling, medical care and other services, if you need them and want them. You may be asked about sex and/or needle -sharing partners and you may be offered help notifying your partners about your positive HIV test. These are all common practices of the health department and apply to all individuals who test positive for HIV.

If you test positive for hepatitis, the Wisconsin health department will be informed of the results. The health department may contact you with resources for counseling and medical care, if you need them and want them. You may be asked about sex and/or needle -sharing partners. These are all common practices of the health department and apply to all individuals who test positive for hepatitis.

Pregnancy Testing in Minors

Urine pregnancy testing will be performed on every female who has begun menstruation (has had at least one period). The first pregnancy test is done to find out if you are eligible for the study. If this first pregnancy test is positive, the study doctor will inform you of the positive pregnancy results and you will not be able to join the study. Results from pregnancy tests done during the study may be reported to you (the minor) and your parent/guardian.

Questionnaires

The Hospital Anxiety and Depression Scale (HADS) questionnaire you will complete in this study may show that you are experiencing symptoms of emotional distress such as depression or anxiety. If the HADS show that you are experiencing depression or anxiety, one of the investigators on the study team will talk with you to find out more information and refer you to a primary care/other physician to work on getting proper diagnosis and treatment if necessary.

Possible Discovery of Findings Related to Medical Imaging

Whenever a CT or X-ray of the lungs is done, there is the chance of finding something unexpected. Unexpected findings can have clear clinical significance, or uncertain clinical significance. Clear clinical

significance means that the CT or X-ray shows a problem that may be treatable and we generally know what the risks are of not treating the problem. Uncertain clinical significance means that the imaging shows something unusual in the brain, but we do not know if it might affect your health, and treatment may not be appropriate or possible. On this study, you will be informed of any findings of clear clinical significance that may be discovered during the imaging procedure, but you will not be informed if there are findings of uncertain clinical significance. In order to assist us in interpreting the results of your CT or X-ray, we are also seeking your permission to review your medical records if you are or have been a patient at this hospital.

There may be benefits to learning such results (such as early detection and treatment of a medical condition), but there are risks as well (such as problems with getting insurance or a job, or feeling worried about a finding for which no treatment is required or appropriate). The CT or X-ray we are using in this research study is not the same quality as a CT or X-ray that you may have as part of your health care. If you believe you are having symptoms that may require clinical imaging, you should contact your primary care physician.

You may also choose to have your physician informed of any findings of clear clinical significance that we report to you by checking the box below. Please note, however, that if you choose to have your physician informed of findings of clinical significance, that report will likely be placed in your medical record.

Please indicate your preference by initialing the appropriate box:

_____ Yes, please inform my doctor of findings of clinical significance – OR –

_____ No, please do not inform my doctor of findings of clinical significance

Name of physician to contact
If you do wish us to report any findings to your physician, you must provide us with the name and location of your primary physician, prior to your CT or X-ray.

My provider's name and clinic are: _____

If you have additional questions about the test results or concerns about your health, contact your primary care provider. You (or your insurance company) will be responsible for costs related to any follow-up care.

The genetic tests that are part of this study are for research purposes only. Because of this, we will not tell you or your doctors the results of these research tests.

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AUTHORIZATION TO USE/DISCLOSE PROTECTED HEALTH INFORMATION

Protected health information (PHI) used in this study

Protected health information, also called PHI, is information about your physical or mental health that includes your name or other information that can identify you, like your date of birth or medical record number. To do this study, we will use the following kinds of PHI:

- Results of tests or procedures done as part of the study
- Things you tell the researchers about your health
- Information currently in your medical records as well as information added to your medical records during the course of this study. This information could include information like your medical history, your diagnosis, and/or your medications. We will get this information from your health care providers such as UW Health.

How will researchers keep my research information confidential?

We have strict rules to protect your personal information and protected health information (PHI). We will limit who has access to your name, address, phone number, and other information that can identify you. We will also store this information securely. The study has a Certificate of Confidentiality from the National Institutes of Health. A Certificate of Confidentiality prohibits researchers from disclosing information or biospecimens that may identify you in a legal proceeding or in response to a legal request without your consent. We may publish and present what we learn from this study, but none of this information will identify you directly without your permission.

However, we cannot promise complete confidentiality. Federal or state laws may permit or require us to show information to university or government officials and to study sponsors responsible for monitoring this study. This includes access to your medical records so that study monitors, auditors, the Institutional Review Board and regulatory authorities can verify study procedures and/or data. These groups will maintain your confidentiality. By signing this consent form, you are authorizing this access to your records. We may also have to tell appropriate authorities, such as child protective services or health care providers, if we learn during the study that you or others are at risk of harm (for example, due to child or elder abuse, or suicidal thoughts).

Authorizing the research team to use your PHI means that we can release it to the people or groups listed in the Privacy section in **Part 1 or 2** for the purposes described in this form. Once your health information is released outside UW-Madison or UW Health it may not be protected by privacy laws and might be shared with others. Also, with appropriate institutional permissions and confidentiality protections, we might use information and biospecimens that we collect during this study for other research or share with other researchers without additional consent or authorization from you or your legally authorized representative.

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Will information from this study go in my medical record?

A medical record will be created for you if you do not already have one. Some of the information we collect for this study will go in your medical record. This includes results of the CT scan and/or chest x-ray, as well as DLCO pulmonary function testing. Results of the HIV, hepatitis B, hepatitis C, and tuberculosis tests will only go in your medical record if they are positive. Both you and your UW Health providers will be able to see results that are placed in your medical record. The following information from research procedures will NOT go in your medical records: physical exams, questionnaires, pulmonary function testing (other than DLCO), and research lab tests.

Study Title: **PrecISE: Precision Interventions for Severe and/or Exacerbation-Prone Asthma Network**
Version Date: **12/09/2021**
Version: **3.0**

This master consent form is not a contract. It is a written explanation of what will happen during the study if you decide to participate. You are not waiving any legal rights by agreeing to participate in this study.

Your signature indicates that this research study has been explained to you, that your questions have been answered, and that you voluntarily agree to participate in this research study.

Participant Signature:

Signature of Participant	Date
Participant's Name – PRINTED	

Legally Authorized Representative's Name and Relationship to Participant, if applicable:

Signature of Legally Authorized Representative	Date
Name of Legally Authorized Representative – PRINTED	Relationship to Participant - PRINTED

Statement of Person Who Obtained Consent

The information in this document has been discussed with the participant or, where appropriate, with the participant's legally authorized representative. The participant has indicated that he or she understands the risks, benefits, and procedures involved with participation in this research study.

Signature of Person who Obtained Consent	Date
Name of Person who Obtained Consent – PRINTED	