Clinical Intervention Study Protocol Template

FULL PROTOCOL TITLE

Ginger's therapeutic potential in Asthma

Study Chairman or Principal Investigator:

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Atrium Innovations (Pure Encapsulations)

Sponsor of IND (IDE):

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Tool Revision History

Version Number: 1.1
Version Date: February 6, 2019
Summary of Revisions Made: None (Original Version)

Version Number: 1.2
Version Date: April 2, 2019
Summary of Revisions Made: An explanation of the randomization has been added and the randomization code will now be held by an independent statistician as opposed to the research pharmacy as suggested by the NCCIH review. We have added the physical locations of where patients will be studied and added locations where blood samples will be analyzed. We have clarified that a 'per protocol' analysis will be used and have defined how subjects will be defined to be compliant with the protocol. Finally we have made additional minor edits to the protocol to respond to ever other comment from NCCIH.

Version Number: 1.3
Version Date: April 24, 2019
Summary of Revisions Made: update 1. Page 8, "Design and Outcomes", this statement has been added: "*The eight subjects will be selected through voluntary participation. The option will be provided to all subjects who sign the consent. Once there have been 4 subjects in Group A and 4 subjects in Group B selected, there will no longer by any additional subjects accepted to join the PK study*."
Update 2. p33, section 9.3 This section is changed to state: "*All randomized subjects will be included in the primary analysis, analyzed based on intention-to-treat. In addition, a secondary analysis based on a per protocol will be conducted. Per protocol analysis will exclude patients who missed 30% or more of their assigned treatment. Please refer to section 5.4 for the equation to calculate compliance*."

Version Number: 1.4
Version Date: May 7, 2019
Summary of Revisions Made: Section 4.1. We have combined elements of inclusion criteria into fewer statements and we have responded to the reviewer's comment in the margin. As requested, we have moved visits 1 and 2 from section 6.2.4 to section 6.2.1. This created some redundancy of statements in section 6.2.1. which has been edited in an attempt to remove the redundancy.

Version Number: 1.5
Version Date: July 22, 2019
Summary of Revisions Made: In response to Westat SIV the following changes were made. Redundancies were removed from section 4.2 that were already accounted for in Section 4.1. Sections 4.1 and 4.2 were then copied into section 6.2 for consistent listing of inclusion/exclusion. In section 10.3.4 we added a deviation for study subjects consuming less than 70% of the study drug. In sections 6.2.4 we corrected the dates for the follow up phone call for visit 4a. We have combined elements of inclusion criteria into fewer statements and we have responded to the reviewer's comment in the margin. As requested, we have moved visits 1 and 2 from section 6.2.4 to section 6.2.1. This created some redundancy of statements in section 6.2.1. which has been edited in an attempt to remove the redundancy.

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STUDY TEAM ROSTER

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PARTICIPATING STUDY SITES

Columbia University Medical Center, The Johns Edsall-John Wood Asthma Center

PRÉCIS

Study Title

Ginger's therapeutic potential in asthma

Objectives

The primary endpoints are the improved tolerance to the bronchoconstrictive effect (reduced airway hyperresponsiveness) of inhaled methacholine (methacholine PD_{20}) or a reduction in exhaled nitric oxide. The secondary endpoints are a reduction in markers of asthmatic lung inflammation; specifically serum cytokines, eosinophilia, and establishing pharmacokinetic parameters of biologically active components of ginger in adult asthmatics.

Design and Outcomes

A placebo controlled, double blind, randomized clinical pilot study of mild to severe asthmatics treated in a 1:1 ratio with oral ginger 1 gm twice per day or matching placebo. This will occur in the Columbia University Medical Center, The Johns Edsall-John Wood Asthma Center Outpatient Unit, 622 West 168th Street, PH 859, New York, NY 10032.

Screening/Run-In Period Adults 18 and older, with physician diagnosed mild to severe persistent asthma will be screened. After reviewing and signing informed consent, subjects that fulfill inclusion and exclusion criteria will be invited to participate.

Day 0/Visit 1: Screening Visit: review of medical history, recording of medication use, physical exam by study MD or NP, scoring on ACT and basic spirometry before and after bronchodilator. Subjects will then be asked to continue their usual asthma medications for the 14-21 day run-in period.

Day 14-21/Visit 2: Subjects will be asked to withhold appropriate medications (long acting bronchodilator for 36 hours, short acting bronchodilator for 6 hours). Women of child bearing potential will have a urine pregnancy test checked. Checklist for methacholine will be reviewed with patient. If ACT remains ≤ 19 and FEV1> 60% predicted, subjects will undergo methacholine bronchoprovocation testing which involves inhaling increasing concentrations of nebulized methacholine until the measured FEV1 decreases by 20% of the initial value measured after diluent inhalation, defined as the methacholine PD20. If ACT is > 19, consistent with good asthma control, subjects will be terminated from the study.

Day 15-23 (1-2 days following V2)/Visit 3 Randomization Visit:
If ACT remains ≤ 19, subjects will be randomized into 2 treatment groups; oral ginger (1g twice per day: Pure Encapsulations™) or matching placebo (*FDA IND in place:* #[redacted]). Ratio of randomization will be 1:1. An independent statistican will generate the randomization codes and allocations. The blinded study coordinator will retrieve the randomization allocation for each subject through RedCap. RedCap is an institutionally available automated system for randomization; the independent statistician will have direct oversight over the process. The blinded study team will not have access to the randomization codes.

At the randomization visit, women of child bearing potential will have a negative pregnancy test confirmed, subjects will be asked to complete an ACT to assess asthma control and a validated asthma quality of life questionnaire (Juniper mini AQLQ). Fractional excretion of nitric oxide (FeNO) will be measured using a Circassia Niox Vero machine with disposable filters. Pre-dose basic spirometry will be performed. 10ml of blood will be collected for measurement of baseline cytokines, biomarkers and blood eosinophil count. Subjects will be given their first dose of study drug and post-dose spirometry will be repeated one hour later.

A total of eight subjects will undergo pharmacokinetic (PK) measurements of the key metabolites of active ginger components. For those patients, an additional 35 ml of blood will be collected over an additional 7 times points (pre-dose, 0.5 hour,1 hour,2 hour,3 hour, 4 hour, and 8 hour). The eight subjects will be selected through voluntary participation. The option will be provided to all subjects who sign the consent. Once there have been 4 subjects in Group A and 4 subjects in Group B selected, there will no longer by any additional subjects accepted to join the PK study.

Day 43-50/Visit 4:. Subjects will be asked to withhold morning dose of the study drug the day of the study visit. Women of child bearing potential will have a negative pregnancy test confirmed. Subjects will be asked to complete an ACT to assess asthma control and a validated asthma quality of life questionnaire (Juniper mini AQLQ). FeNO will be measured using a Circassia Niox Vero machine with disposable filters. Basic spirometry will be performed, Methacholine test will be performed if subject meets safety criteria (FEV1>1.5L or 60% predicted). 10ml of blood will be collected for measurement of cytokines, biomarkers and blood eosinophil count. For those patients in PK group, an additional 35 ml of blood will be collected over an additional 7 times points (pre-dose, 0.5 hour,1 hour,2 hour,3 hour, 4 hour, and 8 hour). Study drug will be administered in the clinic after the pre-dose PK blood draw.

Unused study medication will be collected and pill count will be recorded.

Day 71-78/Visit 5: Subjects will be asked to withhold morning dose of the study drug the day of the study visit. Women of child bearing potential will have a negative pregnancy test confirmed. Subjects will be asked to complete an ACT to assess asthma control and a validated asthma quality of life questionnaire (Juniper mini AQLQ). FeNO will be measured using a Circassia Niox Vero machine with disposable filters. Basic spirometry will be performed. Methacholine hyperresponsiveness will be measured if subject meets safety criteria (FEV1 > 1.5L or >60% predicted). 10ml of blood will be collected for measurement of cytokines, biomarkers and blood eosinophil count. For those patients in PK group, an additional 35 ml of blood will be collected over an additional 7 times points (pre-dose,0.5 hour,1 hour,2 hour,3 hour, 4 hour, and 8 hour). Unused study medication will be collected and pill count will be recorded. Study drug will be administered in the clinic after the pre-dose PK blood draw.

Sample Size and Population

Adults 18 and older, with physician diagnosed mild to severe persistent asthma will be screened. 36 participants will be randomized equally into two arms (18 per group); 1 gram of oral ginger extract twice a day for 28 days or matching placebo. Our sample size analysis requires 16 participant per group and with an anticipated 10% attrition rate, we will enroll 18/group.

Randomization will not be stratified in this pilot study.

The NIH National Asthma Education and Prevention Program (NAEPP) Guidelines for assessing asthma severity will be used by the PI to grade severity of asthma.[1]

1. STUDY OBJECTIVES

1.1 Primary Objective

The primary endpoints are a clinically significant improvement in tolerance to inhaled methacholine (PD20) or a clinically significant decrease in exhaled nitric oxide. A clinically significant increase in tolerance to inhaled methacholine is defined as a 0.7 increase in the doubling dose for inhaled methacholine from the subjects baseline. A clinically significant decrease in exhaled nitric oxide is defined as a 20% decrease in subjects starting at a baseline of >50 ppb or a decrease of 10 ppb for subjects starting at a baseline of <50 ppb.

1.2 Secondary Objectives

a. To determine if oral daily ginger extract intake;
   1. increases forced expiratory volume in one second (FEV1) by 100ml.
   2. decreases blood eosinophilia
   3. decreases asthma-associated cytokines in serum

b. Establish pharmacokinetic parameters of biologically active components of ginger in adult asthmatics.

2. BACKGROUND AND RATIONALE

2.1 Background on Condition, Disease, or Other Primary Study Focus

The Centers for Disease Prevention and Control report that 9% of Americans have asthma which accounted for 1.8 million emergency room visits and 0.5 million hospitalizations in 2011 with a projected cost of $56 billion.[2] Asthma is a chronic inflammatory disorder of the airways characterized by bronchoconstriction and airway inflammation marked by airway hyperresponsiveness. Current asthma therapies include short- and long-acting β-agonists to combat bronchoconstriction and inhaled corticosteroids (ICS) to reduce airway inflammation. These medications have important adverse effects, are not suitable for some patients, and have poor adherence.[3] There are emerging targeted biologic therapies, especially directed against the Th2-high endotype of asthma, but these therapies are aimed at patients with severe asthma, are expensive, and do not address the multiple endotypes of asthma. Consequently, many Americans have increasingly turned towards complementary and alternative medicines for treating asthma.

Recent studies found that 60% of moderate asthmatics and 70% of severe asthmatics report using complementary and alternative (CAM) therapies to self-treat their asthma symptoms.[4] Natural plant products in the forms of teas, topical ointments, and dietary supplements have been used for the relief of respiratory ailments including cough and bronchospasm.[5] Of the many types of CAM therapies chosen by asthmatics, as many as 40% of asthmatics use herbal therapies to self-treat their asthma symptoms.[4] The exact mechanism of action of these agents is unclear but may involve attenuation of the allergic cascade through blockade of IgE mediated inflammation, anti-inflammatory and antioxidant effects, and/or direct effects on acutely relaxing human airway smooth muscle (ASM).

2.2 Study Rationale

Recently we demonstrated that purified components of ginger (6-shogaol, 6-gingerol, 8-gingerol*)* acutely relaxed human airway smooth muscle (ASM) in vitro[6] and our newest preliminary data shows that specific human metabolites of these components have potent ASM relaxing properties. Additionally, we have preliminary data showing that ginger components reduced lung inflammation in a mouse model of asthma. We demonstrated that the cellular mechanism by which ASM relaxation occurs is via inhibition of phospholipase C (PLC) a pivotal enzyme that mediates smooth muscle contraction as well as cytokine release from immune cells and airway structural cells.[6] Thus, natural compounds that inhibit PLC can

target two key features of the pathophysiology of asthma; smooth muscle constriction and cytokine release. It is not possible to measure PLC activity directly in live human subjects, but it is possible to directly measure the functional effect of PLC inhibition; improved tolerance for inhaled methacholine and reduced inflammation which will be the key biological signatures measured in this 2 month clinical study of oral ginger in asthmatics. We contend that this proposal is highly responsive to the goals of this program as it (1) studies a natural product in a disease commonly encountered in primary care practice; (2) tests a natural botanical substance widely used as a dietary supplement for which sufficient early stage safety and mechanistic data justifies further clinical testing; (3) measures the bioavailability of the natural product and its major human metabolites; and (4) demonstrates primary biological signatures in patients.

Ginger is widely used as an over-the-counter oral dietary supplement. The formulation and amount of ginger used in this study (2g per day; Pure Encapsulations®) has been chemically characterized by HPLC and has been administered to patients at the oral amount (2 grams) for 28 days in multiple human studies measuring inflammatory mediators in colonic mucosal biopsies. We chose this formulation and dose based on its history of excellent tolerance in previous human studies. We chose to divide the 2g dose into 1g twice a day dosing to minimize the chance of gastrointestinal side effects while limiting the burden on subject dosing to twice a day to increase retention and compliance within the study. We have also demonstrated in pre-clinical studies in a mouse model of asthma that this dose reduces asthma-associated lung inflammation.

The incidence of side effects in a 28 day trials of 30 individuals were not significantly different in placebo versus ginger and no adverse events were greater than the NCI Common Toxicity Criteria Grade 1. In a second study of 27 individuals, no adverse event greater than NCI Common Toxicity Criteria Grade 1 was reported (no placebo comparison) and the leading complaints were gastrointestinal symptoms of eructation, heartburn or indigestion.[7] In a third study of 20 patients consuming the same formulation in the same amount for the same duration (2g, Pure Formulations, 28 days) no statistically significant increase in adverse events occurred compared to placebo, no toxicities were greater than the NCI Common Toxicity Criteria Grade 1 and included bloating, nausea and heartburn.

There have been small numbers of studies reporting on possible inhibition of platelet aggregation by ginger. Ginger has been shown an in vitro study to inhibit platelet aggregation with a potency similar to that of aspirin and in another study of human volunteers, to have a syngergistic effect with nifedipine in platelet aggregation.[8-10] A single case report has been published demonstrating epistaxis in a women who was being treated with Coumadin who subsequently started taking ginger.[11] Subjects taking anti-coagulation will be excluded from participation, though subjects taking aspirin alone will be included in the study since there have been no studies or reports of increased bleeding risk with aspirin and ginger combined.

3. STUDY DESIGN

A placebo controlled, double blind, randomized clinical pilot study of mild to severe asthmatics treated in a 1:1 ratio with oral ginger 1 gm twice per day or matching placebo.

18 subjects will be assigned to each of two arms (ginger vs. placebo). This is defined by a power analysis requiring 16 subjects per arm and a 10% projected attrition rate. Subjects will be evaluated 5 times during the study, at screening, baseline methacholine testing, at the initial randomization visit and at days 28 and 56 while taking ginger or placebo.

The primary outcomes will be the improved tolerance to the bronchoconstrictive effect (reduced airway hyperresponsiveness) of inhaled methacholine (methacholine PD_{20}) or a reduction in exhaled nitric oxide. Secondary outcomes will include an improvement in baseline FEV1 of 100ml, a reduction in eosinophilia or a reduction in asthma associated serum cytokines. An additional secondary outcome will be defining the pharmacokinetic profile of active components of ginger in adult asthmatics.

Grant phase	Spec. Aim	Primary outcome	Clinically Significant Change [ref]	Means ± S.D; examples from literature [ref] (units)	Sample Size \group	# of groups	Sample size required	Sample Size required with 10% attrition
R61	1	Mch PD_{20} doubling dose	Increase of 0.7 in Mch doubling dose[12]	1.07 ± 0.6 1.73 ± 0.6 (Mch doubling dose)[12]	14	2 2g/day ginger placebo	28	32
	2	Exhaled nitric oxide	20% decr for >50 ppb or decr of 10ppb for <50ppb[13]	74 ± 37 37 ± 34 (ppb)[14]	16	2 2g/day ginger placebo	32	36 for aims 1&2

Outpatient; The John Edsall-John Wood Asthma Center at the Columbia University Medical Center

Individual enrollment: 78 +/- 7 days. Enrollment period 12 months, Entire trial (first subject screened to last patient completed): 20 months.

Screening/Run-In Period

Adults 18 and older, with physician diagnosed mild to severe persistent asthma will be screened. After reviewing and signing informed consent, subjects that fulfill inclusion and exclusion criteria will be invited to participate.

Day 0/Visit 1: Screening Visit: review of medical history, recording of medication use, physical exam by study MD or NP, scoring on ACT and basic spirometry before and after bronchodilator. Subjects will then be asked to continue their usual asthma medications for the 14-21 day run-in period.

Day 14-21/Visit 2: Subjects will be asked to withhold appropriate short and long acting bronchodilators for the appropriate period. Women of child bearing potential will have a urine pregnancy test checked. Checklist for methacholine will be reviewed with patient. If ACT remains ≤ 19 and FEV1> 60% predicted, subjects will undergo methacholine bronchoprovocation testing which involves inhaling increasing concentrations of nebulized methacholine until the measured FEV1 decreases by 20% of the initial value measured after diluent inhalation, defined as the methacholine PD20. If ACT is > 19, consistent with good asthma control, subjects will be terminated from the study.

Day 15-23 (1-2 days following V2)/Visit 3 Randomization Visit:
If ACT remains ≤ 19, subjects will be randomized into one of two treatment groups; oral ginger (1g twice per day: Pure Encapsulations™) or matching placebo (*FDA IND in place:* #[redacted]). Ratio of randomization will be 1:1.

At the randomization visitwomen of child bearing potential will have a negative pregnancy test confirmed, subjects will be asked to complete an ACT to assess asthma control and a validated asthma quality of life questionnaire (Juniper mini AQLQ). Fractional excretion of nitric oxide (FeNO) will be measured using a Circassia Niox Vero machine with disposable filters. Pre-dose basic spirometry will be performed. 10ml of blood will be collected for measurement of baseline cytokines, biomarkers and blood eosinophil count. Subjects will be given their first dose of study drug and post-dose spirometry will be repeated one hour later.

A subset of subjects (4 males and 4 females) will undergo pharmacokinetic (PK) measurements of the key metabolites of active ginger components. For those patients, an additional 35 ml of blood will be collected over an additional 7 times points (pre-dose, 0.5 hour,1 hour,2 hour,3 hour, 4 hour, and 8 hour).

Day 43-50/Visit 4:. Subjects will be asked to withhold morning dose of the study drug the day of the study visit. Women of child bearing potential will have a negative urine pregnancy test confirmed. Subjects will be asked to complete an ACT to assess asthma control and a validated asthma quality of life questionnaire (Juniper mini AQLQ). FeNO will be measured using a Circassia Niox Vero machine with disposable filters. Basic spirometry will be performed, Methacholine test will be performed if subject meets safety criteria (FEV1>1.5L or 60% predicted). 10ml of blood will be collected for measurement of cytokines, biomarkers and blood eosinophil count. For those patients in PK group, an additional 35 ml of blood will be collected over an additional 7 times points (pre-dose, 0.5 hour,1 hour,2 hour,3 hour, 4 hour, and 8 hour). Study drug will be administered in the clinic after the pre-dose PK blood draw.

Unused study medication will be collected and pill count will be recorded.

Day 71-78/Visit 5: Subjects will be asked to withhold morning dose of the study drug the day of the study visit. Women of child bearing potential will have a negative pregnancy test confirmed. Subjects will be asked to complete an ACT to assess asthma control and a validated asthma quality of life questionnaire (Juniper mini AQLQ). FeNO will be measured using a Circassia Niox Vero machine with disposable filters. Basic spirometry will be performed. Methacholine hyperresponsiveness will be measured if subject meets safety criteria (FEV1 > 1.5L or >60% predicted). 10ml of blood will be collected for measurement of cytokines, biomarkers and blood eosinophil count. For those patients in PK group, an additional 35 ml of blood will be collected over an additional 7 times points (pre-dose,0.5 hour,1 hour,2 hour,3 hour, 4 hour, and 8 hour). Unused study medication will be collected and pill count will be recorded. Study drug will be administered in the clinic after the pre-dose PK blood draw.

Randomization is a process that assigns participants/subjects by chance (rather than by choice) into specific groups, typically for clinical research and clinical trials. An independent statistican will generate the randomization codes and allocations. The blinded study coordinator will retrieve the randomization allocation through RedCap at the time of the randomization visit.. RedCap is an institutionally available automated system for randomization; the independent statistician will have direct oversight over the process. The blinded study team will not have access to the randomization codes. In this module, randomization model is defined as Drug A and Drug B in a 1:1 ratio. Drug A and Drug B may refer to placebo or active drug, however they are left coded as such to ensure blinding. The module creates a template allocation table, which the user uses to structure the randomization table to be imported. The module also monitors the overall allocation progress and assignment of randomized subjects to ensure equal proportions of active drug and placebo. Only one site member will be allowed randomization privileges, but the site will confirm, and lock the specific data field to ensure that no data is altered after randomization. There is no stratification, and there are no variable block sizes.

All evaluations and blood draws will be completed at a single site at a single center, the outpatient clinic of The John Edsall-John Wood Asthma Center at the Columbia University Medical Center. Blood eosinophils will be measured by the Center for Advanced Laboratory Medicine (CALM) with the Department of Pathology and Cell Biology at Columbia University Medical Center. Plasma cytokines will be measured by multiplex array in the laboratory of Charles Emala, at Columbia University and the metabolite measurements within the PK studies will be performed by Shengmin Sang, PhD , Suite 4222, UNC Nutrition Research Building, NCRC, 500 Laureate Way, Kannapolis, NC 28081.

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4. SELECTION AND ENROLLMENT OF PARTICIPANTS

4.1 Inclusion Criteria

Subjects must meet all of the inclusion criteria to participate in this study.

1. Adults aged 18 years and above, with mild to severe persistent asthma will be enrolled as defined by The NIH National Asthma Education and Prevention Program (NAEPP) Guidelines for Assessing Asthma Severity[1] (please see table page 9). Subjects will have asthma which is not optimally controlled as defined by Asthma Control Test (ACT) score, despite the current use of inhaled corticosteroids with or without inhaled long-acting beta agonists.
2. Treatment with inhaled corticosteroids (ICS) +/- long acting β-agonists/long acting muscarinics and montelukast;
3. Physician diagnosed asthma, confirmed by patient history/report, as well as pulmonary function test (FEV1 ≥60% of predicted or 1.5 L) and methacholine testing (Baseline methacholine PD20 < 16 mg/ml if taking ICS or < 8 mg/ml if not taking ICS at Visit 2) to confirm diagnosis.
4. Non-smoker (e.g., tobacco, e-cigarette, marijuana) for ≥1 yr.; Nicotine patch or gum is allowed.
5. ≤10 pack-year smoking history;
6. Suboptimal control of asthma as determined by a score < 19 or less on the Asthma Control Test (ACT) at Screening and Randomization Visits.
7. Ability to understand the English or Spanish language and to understand the study procedures and comply with them for the entire study period.
8. Females of childbearing potential: Pregnant or lactating; participants of appropriate age will be screened with urine pregnancy tests at each visit and cannot participate if pregnant. Participants must agree to use effective contraception during the trial.
9.

Prior Medical Therapy

Washouts:
The chart below lists medications/substances that decrease airway hyper-responsiveness and should not be taken prior to pulmonary function testing. Withholding times are listed next to the medication.

Medications/Substances	Withhold/Washout Times before test
Caffeine, cola drinks, and chocolate	Avoid the day of
Alcohol	4hrs
Short-acting β-agonists in conventional inhaled doses (e.g. albuterol 200 μg)	6 hrs
Long-acting β-agonists (e.g. salmeterol)	36 hrs
Ipratropium (Atrovent 40 μg)	12 hrs
Long-acting anti-muscarinic agents (e.g. tiotropium)	⩾168 hrs (7days)
Ultra-long-acting β-agonists (i.e. indacaterol, vilanterol, olodaterol) Oral theophylline	24-48 hours (2 days)
Oral theophylline	12-24 Hrs

4.2 Exclusion Criteria

Subjects with any of the exclusion criteria will be excluded from study participation.

1. Other major chronic illnesses: Conditions which in the judgment of the study physician would interfere with participation in the study, e.g., non-skin cancer, uncontrolled diabetes mellitus, coronary artery disease, congestive heart failure, stroke, severe hypertension, renal failure, liver disorders, malabsorption disorders, immunodeficiency states, major neuropsychiatric disorder;
2. Cardiovascular problems:
    a. Myocardial infarction or stroke in last 3 months
    b. Uncontrolled hypertension
    c. Known aortic aneurysm
3. History of physician diagnosis of chronic bronchitis, emphysema or COPD
4. Medication use:
    a. Current consumption of ginger supplements
    b. oral corticosteroid use within the past 6 weeks
    c. use of an investigational treatment in the previous 30 days
    d. Use of anti-coagulation such as warfarin, rivaroxaban and similar agents.
5. Known adverse reaction to ginger or ginger products
6. Subjects with cancer, other than skin cancer, will be excluded.
7. Current drug or alcohol use or dependence that, in the opinion of the site investigator, would interfere with adherence to study requirements
8. Inability or unwillingness of individual or legal guardian/representative to give written informed consent.

4.3 Study Enrollment Procedures

Participants will be recruited by a variety of methods that have been used previously by the study team. These methods may include solicitation in physician offices, clinics, workplaces, and public media advertisements. All public advertisements will first be approved by the Institutional Review Board (IRB).

Potential enrollees will be approached either in person, by telephone or by mail to establish general eligibility criteria.

Documentation of ineligibility and non-participation of eligible candidates will be recorded within a screening log.

Potential enrollees will meet with the study Coordinator and local physician co-investigators to review the study in a quiet room and will be given as much time as needed to read the consent and ask questions. The consents, HIPAA Authorization and all study questionnaires will be available in English and Spanish. If they agree to participate, they will be asked to sign a consent. A copy of the consent form will be given to each participant, and the signed original will be kept in the participant's research chart. Only participants who are capable of providing their own informed consent will be enrolled.

Randomization is a process that assigns participants/subjects by chance (rather than by choice) into specific groups, typically for clinical research and clinical trials. An independent statistican will generate the randomization codes and allocations. The blinded study coordinator will retrieve the randomization allocation through RedCap. RedCap is an institutionally available automated system for randomization and the statistician will have direct oversight over the process. The blinded study team will not have access to the randomization codes. In this module, randomization model is defined as Drug A and Drug B in a 1:1 ratio. Drug A and Drug B may refer to placebo or active drug, however they are left coded as such to ensure blinding. The module creates a template allocation table, which the user uses to structure the randomization table to be imported. The module also monitors the overall allocation progress and assignment of randomized subjects to ensure equal proportions of active drug and placebo. Only one site

member will be allowed randomization priviledges, but the site will confirm, and lock the specific data field to ensure that no data is altered after randomization. There is no stratification, and there are no variable block sizes.

5. STUDY INTERVENTIONS

5.1 Interventions, Administration, and Duration

A 28-day supply of study drug (ginger capsules) or placebo (matching capsules) will be dispensed from the Columbia University Medical Center research pharmacy in a blinded fashion and distributed to the study subjects by the clinical research coordinator in the asthma clinic. Patients will take their first dose of study drug at the study site during the randomization visit and will then be instructed to take 1g twice a day with meals in the outpatient setting. Patients participating in the pharmacokinetic studies will be told to hold their daily dose on subsequent clinic visit dates until timed dosing occurs in the clinic.

Potential Adverse Events*;* Ginger is widely used as an over-the-counter dietary supplement. The formulation and amount of ginger used in this study (2g per day; Pure Encapsulations®) has been chemically characterized by HPLC and has been administered to patients at the oral amount (2 grams) for 28 days in multiple human studies measuring inflammatory mediators in colonic mucosal biopsies. The incidence of side effects in a 28 day trials of 30 individuals were not significantly different in placebo versus ginger and no adverse events were greater than the NCI Common Toxicity Criteria Grade 1. In a second study of 27 individuals no adverse event greater than NCI Common Toxicity Criteria Grade 1 was reported (no placebo comparison) and the leading complaints were gastrointestinal symptoms of eructation, heartburn or indigestion.[15] In a third study of 20 patients consuming the same formulation in the same amount for the same duration (2g, Pure Formulations, 28 days) no statistically significant increase in adverse events occurred compared to placebo, no toxicities were greater than the NCI Common Toxicity Criteria Grade 1 and included bloating, nausea and heartburn.

There have been small numbers of studies reporting on possible inhibition of platelet aggregation by ginger. Ginger has been shown an in vitro study to inhibit platelet aggregation with a potency similar to that of aspirin and in another study of human volunteers, to have a syngergistic effect with nifedipine in platelet aggregation.[8-10] A single case report has been published demonstrating epistaxis in a women who was being treated with Coumadin who subsequently started taking ginger.[11] Subjects taking anti-coagulation will be excluded from participation, though subjects taking aspirin alone will be included in the study since there have been no studies or reports of increased bleeding risk with aspirin and ginger combined.

Available Supportive Care: A bronchodilator (albuterol/salbuterol) will be available to be administered if the participant is uncomfortable from the effects of the methacholine challenge test. A physician or nurse practitioner will be available during all methacholine tests.

There is no dose escalation component to this study.

No modification to the study interventions will be employed without prior review and approval of the NCCIH, FDA, IRB and DSMB. The leading expected complaints associated with oral ginger consumption are gastrointestinal symptoms of eructation, heartburn or indigestion. We will utilize the National Cancer Institute Common Toxicity Criteria (CTCAE) Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2 Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.
Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL.
Grade 4 Life-threatening consequences; urgent intervention indicated.

Grade 5 Death related to AE.
FDA IND approves the administration of this dietary supplement from Pure Encapsulations at a dose of 2g/day for a duration of 56 days. No changes in these parameters are anticipated.

5.2 Handling of Study Interventions

The study drug (~500mg capsules) (ginger extract from Pure Encapsulations) and matching placebo have been provided to our research pharmacy and packaged (120 capsules/bottle) by the manufacturer. Each bottle is labeled 'A' or 'B' and the code is held by the research pharmacy. Study drug is stored at room temperature; temperature logs are maintained by Research Pharmacy. For distribution to study subjects, the clinical research coordinator will obtain the appropriately labeled bottle from the research pharmacy on the day of the study visit and distribute to the subject. Unused study drugs and placebo will be destroyed.

Study intervention accountability records will be the case report source documents that will be stored within the study binder and include (1) inclusion/exclusion documentation; (2) medical history; (3) concomitant medications; (4) adverse events; (5) methacholine challenge data; (6) individual source documents for visits 1-5.

There are no lifestyle/behavioral interventions in this study. Not applicable.

The placebo is in an identically appearing capsule as the study compound. Taste of placebo and ginger is matched as per manufacturer.

5.3 Concomitant Interventions

Required medications: Inhaled corticosteroids with or without long-acting beta agonists.
Allowed medications: Long acting anti-muscarinics, montelukast, or other medications not specifically excluded.
Prohibited medications: anti-coagulants such as warfarin, rivaroxaban and similar agents

5.3.1 Allowed Interventions

Subjects will continue their usual asthma medications during the study except for the washout periods listed in section 4.1. Patients will continue their inhaled corticosteroids with or without inhaled long acting beta agonists and/or long acting anti-muscarinic medications. Additional asthma medications (e.g. montelukast) are also allowed. Rescue of asthma symptoms with short-acting beta agonists is also allowed and if this occurs within a washout period, the study visit will be re-scheduled. Subjects who are not excluded due to the use of anti-coagulants will continue the use of all other prescribed medications.

5.3.2 Required Interventions

No other required interventions.

5.3.3 Prohibited Interventions

Subjects prescribed anti-coagulants (warfarin, rivaroxaban and similar agents) are excluded from participating in the study and are prohibited while the participant is in the study.

5.4 Adherence Assessment

Adherence will be recorded by pill counts at the 28 day and 56 day visit. Adherence will be defined by at least 70% of the capsules consumed. Compliance will be calculated as such:

Number of doses taken by the subject = Number of pills dispensed – number of pills returned

Number of doses expected = will be calculcated by the SC based on the date of visit and original date dispensed, times the number of pills that should be taken per day

$$Adherence = 100 - \left(\left(\frac{Number\ of\ doses\ expected - \ number\ of\ doses\ taken\ by\ the\ subject}{number\ of\ doses\ expected} \right) * 100 \right)$$

6. STUDY PROCEDURES

6.1 Schedule of Evaluations

Assessment	Screening: Visit 1 (Day 1)	Baseline, Enrollment Visit 2 (Day 14-21)	Study & Randomization Visit 3 (Day 15-22)	Study Visit Visit 4 (Day 43-50)	Study Visit Visit 5 (Day 71-78)
Informed Consent Form	X				
Demographics	X				
Administer Asthma Control Test (ACT)	X	X	X	X	X
Administer QOL questionnaire			X	X	X
Administer 2 week recall questionnaire			X	X	X
Confirm Medication Washouts	X	X	X	X	X
Medical History	X		X		
General Physical Examination	X		X	X	X
Urine pregnancy test for women of childbearing age	X		X	X	X
Inclusion/Exclusion Criteria	X		X		
Vital Signs	X		X	X	X
Spirometry	X	X	X	X	X
Post-Bronchodilator Spirometry	X				
Methacholine Bronchoprovocation		X		X	X
Administer bronchodilator	X	X		X	X
Methacholine Recovery challenge		X		X	X
GI side effects checklist			X	X	X
Measure exhaled nitric oxide			X	X	X
Blood draw for cytokines, eosinophilia, biomarkers			X	X	X
Enrollment/Randomization			X		
Pre-dose blood draw for PK subjects			X	X	X
Administer dose of study drug			X	X	X
Post dose spirometry (1hr)			X		
PK blood draws for selected subjects			X	X	X
Dispense drug			X	X	
IP Accountability				X	X
Concomitant Medications	X	X	X	X	X
Adverse Events	X	X	X	X	X

6.2 Description of Evaluations

Informed Consent Form: If the potential enrollees are interested in participating, they will meet with the study Coordinator and local physician co-investigators to review the study and to ask questions. They will be asked to sign consent. A copy of the consent form will be given to each participant, and the signed original will be kept in the participant's research chart. Only participants who are capable of providing their own informed consent will be enrolled. The consents, HIPAA Authorization and all study questionnaires will be available in English and Spanish.

Demographics: Collection will include age, gender, race, education and zip code.

Asthma Control Test (ACT): Asthma symptom score will be measured with the Asthma Control Test at all visits. This instrument, which has been validated for ages 12-84 years, is a5 question, 4-week recall questionnaire that addresses issues of asthma control, symptoms, and nocturnal awakenings.

Juniper mini-Asthma specific quality of life (QOL)*:* Asthma specific quality of life is measured with instruments developed and validated by Juniper, Guyatt and colleagues.

Asthma Two Week Recall: The Asthma two week recall (A2WR) was developed to capture the inherent intensity of the disease in individuals with asthma. It quantifies severity by combining information about impairment, risk, and the amount of medication required to maintain control.

Confirm Medication Washouts**:** Cessation of medications will be confirmed at study visits as described in the table in section 4.1. If inadequate washouts have not occurred, the study visit will be re-scheduled.

Medical History: Relevant medical history, including history of current disease, other pertinent respiratory history, and information regarding underlying diseases will be recorded at the Screening visit and confirmed during the randomization visit.

General Physical Exam: A complete physical examination will be performed by either the Investigator or a Sub-Investigator as indicated on the Schedule of Events. Complete physical examinations will include a minimum of a review of the subject's general appearance, head, eyes, ears, nose, and throat (HEENT), neck, heart, lungs, abdomen, extremities, skin, and general neurological system. Symptom-oriented or brief physical examinations will be performed at time points noted in the Schedule of Events and as clinically indicated. New abnormal physical exam findings not present during the follow up visits will be recorded as AEs and followed during subsequent visits.

Concurrent Medications/therapies: Will be documented throughout the course of the study. Dose, route, unit frequency of administration, and indication for administration and dates of medication will be captured.

Urine Pregnancy Test: A urine pregnancy test will be obtained from female subjects who are of childbearing age prior to their participation and at every study visit in this study.

Inclusion/Exclusion Criteria:
Inclusion Criteria**:**
Subjects must meet all of the inclusion criteria to participate in this study.

1. Adults aged 18 years and above, with mild to severe persistent asthma will be enrolled as defined by The NIH National Asthma Education and Prevention Program (NAEPP) Guidelines for Assessing Asthma Severity[1] (please see table page 9). Subjects will have asthma which is not optimally controlled as defined by Asthma Control Test (ACT) score, despite the current use of inhaled corticosteroids with or without inhaled long-acting beta agonists.
2. Treatment with inhaled corticosteroids (ICS) +/- long acting β-agonists/long acting muscarinics and montelukast;

3. Physician diagnosed asthma, confirmed by patient history/report, as well as pulmonary function test (FEV1 ≥60% of predicted or 1.5 L) and methacholine testing (Baseline methacholine PD20 < 16 mg/ml if taking ICS or < 8 mg/ml if not taking ICS at Visit 2) to confirm diagnosis.
4. Non-smoker (e.g., tobacco, e-cigarette, marijuana) for ≥1 yr.; Nicotine patch or gum is allowed.
5. ≤10 pack-year smoking history;
6. Suboptimal control of asthma as determined by a score < 19 or less on the Asthma Control Test (ACT) at Screening and Randomization Visits.
7. Ability to understand the English or Spanish language and to understand the study procedures and comply with them for the entire study period.
8. Females of childbearing potential: Pregnant or lactating; participants of appropriate age will be screened with urine pregnancy tests at each visit and cannot participate if pregnant. Participants must agree to use effective contraception during the trial.

Exclusion Criteria:
Subjects with any of the exclusion criteria will be excluded from study participation.

1. Other major chronic illnesses: Conditions which in the judgment of the study physician would interfere with participation in the study, e.g., non-skin cancer, uncontrolled diabetes mellitus, coronary artery disease, congestive heart failure, stroke, severe hypertension, renal failure, liver disorders, malabsorption disorders, immunodeficiency states, major neuropsychiatric disorder;
2. Cardiovascular problems:
    a. Myocardial infarction or stroke in last 3 months
    b. Uncontrolled hypertension
    c. Known aortic aneurysm
3. History of physician diagnosis of chronic bronchitis, emphysema or COPD
4. Medication use:
    d. Current consumption of ginger supplements
    e. oral corticosteroid use within the past 6 weeks
    f. use of an investigational treatment in the previous 30 days
    g. Use of anti-coagulation such as warfarin, rivaroxaban and similar agents.
5. Known adverse reaction to ginger or ginger products
6. Subjects with cancer, other than skin cancer, will be excluded.
7. Current drug or alcohol use or dependence that, in the opinion of the site investigator, would interfere with adherence to study requirements
8. Inability or unwillingness of individual or legal guardian/representative to give written informed consent.

Vital Signs: Height, weight, smoking status, number of pack years will be collected at the screening visit. Measurement of body temperature, blood pressure, pulse, SpO2 and respirations will be performed after resting for 5 minutes at every visit.

Spirometry: **S**ubjects will be asked to perform pulmonary function testing for collection of lung function data at each visit. Pulmonary function testing will be performed according to American Thoracic Society (ATS) guidelines (2005). Subjects will be tested using the same spirometry equipment at every visit. Up to 8 efforts will be performed to obtain 3 acceptable and reproducible test results. The best results from the 3 acceptable and reproducible efforts for PFTs will be recorded on the subject's case report form and a copy of the spirometry reports will be retained with the subject's source documents.

Post-Bronchodilator Spirometry: Will be performed 15 mins after inhalation of 4 puffs of a short acting Bronchodilator.

Methacholine Provocation: A methacholine challenge test is a medical test used to assist in the diagnosis of asthma. The patient breathes in nebulized methacholine at gradually increasing doubling doses, starting with diluent only. Methacholine provokes bronchoconstriction, or narrowing of the airways via M3 receptors. The degree of narrowing can then be quantified by spirometry which is performed after inhalation of each dose. Once the FEV1 drops by 20% or more from baseline diluent spirometry, the test in halted.

Methacholine Recovery Challenge Albuterol will be administered by inhalation (4 puffs) at the end of the methacholine provocation test to return the patients FEV1 back to baseline***:***

GI side effect checklist: Patients will be asked about the frequency and severity of GI symptoms including eructation, heartburn, nausea, bloating or indigestion at Visits 3,4 and 5.

Measured Exhaled Nitric Oxide (FeNO): FeNO is widely used as a global measure of lung inflammation. Exhaled breath will be collected from forced expirations using disposable mouthpieces for the online exhaled NO (Circassia) procedure described in the American Thoracic Society (ATS) guidelines. FeNO levels will be measured at Visits 3,4 and 5.

Blood Draw for Cytokines, eosinophilia, biomarkers: Peripheral venous blood venous blood will be collected at Visit 3, 4 and 5 for the measurement eosinophils and cytokines and biomarkers. 8 subjects will also have blood collected for pharmacokinetic studies. Eosinophils counts will be measured in the Center for Advanced Laboratory Medicine (CALM) lab in the Department of Pathology at Columbia University located at 622 West 168th St. PH 7-200, New York, NY 10032. Multiplex cytokine analyses will be performed in the laboratory of Charles Emala, MD, Department of Anesthesiology, 650 West 168th, Black Building Room 713, New York, NY 10032.

Enrollment/Randomization: Randomization to either ginger capsules or placebo will be done using an randomization algorithm within REDCap in a blinded fashion (group A or B).

Pre-Dose blood draw for PK subjects: Study drug should be withheld the day of the study visit for the PK subgroup. Study drug will be administered in the clinic after the pre-dose PK blood draw

Administer Study Drug: At the randomization visit, subjects will receive 2 capsules of either ginger extract (~500mg) or identical appearing placebo based on their randomization group.

Post-Dose Spirometry (1hr): On visit 3, Subjects will repeat spirometry 1 hr after the ingestion of 2 capsules of ginger extract (~500mg capsules) or two capsules of placebo to determine if there is an acute bronchodilatory benefit of ginger.

PK blood draws for PK subjects: **Pharmacokinetic (PK) Measurements:**
Subject plasma will be obtained for the measurement of PK measurements at Visit 3, Visit 4, and Visit 5 from a group of 8 subjects (4 Males & 4 Females). Serum samples will be collected at the following time points before and after the oral ingestion of 1g ginger; *At Day 1, 28 & 56*: Pre Dosing (time 0), Post Dosing 0.5, 1, 2,3, 4,& 8 hrs. We will quantify major metabolites of 6-shogaol (i.e. M2, M6, M9, and M11) and major metabolites of 6-gingerol (6-gingerdiols). Samples will be aliquoted and stored in such a manner that additional metabolites of these ginger components and additional ginger components (8-shogoal, 10-shogaol, 8-gingerol, 10-gingerol) and their metabolites can be evaluated in future studies. Samples will be processed, aliquoted and stored in the research laboratory of Charles Emala (Black building room 713;650 West 168th St., New York, NY 10032. Plasma samples will be shipped on dry ice to the laboratory of Shengmin Sang, PhD at Suite 4222, UNC Nutrition Research Building, NCRC, 500 Laureate Way, Kannapolis, NC 28081.

Dispense Drug: Capsules containing ginger extract (~500mg) or placebo will be ingested by the patient at a recorded time at the randomization visit to allow for 1hr post-spirometry and PK measurements in selected subjects. Drug will also be dispensed at visit 4.

Pill Count: At study visits 4 and 5 pill counts will be recorded to document compliance with the study drug or placebo.

Concomitant Medications: All current medications will be recorded including dose and last time taken.

Adverse Events: Definition of adverse event/serious adverse event: An Adverse Event (AE) is any unfavorable and unintended symptom, or disease temporally associated with the administration of ginger or the clinical testing proposed that may or may not be considered related to the medical treatment or procedure.
Classification of adverse event severity: We will utilize the National Cancer Institute Common Toxicity Criteria (CTCAE) Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2 Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.
Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL.
Grade 4 Life-threatening consequences; urgent intervention indicated.
Grade 5 Death related to AE.

Reporting of Serious Adverse Events A serious adverse event (SAE) is defined by federal regulation as any AE occurring at any dose that results in any of the following outcomes: death, life-threatening AE, hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Serious adverse events occurring after signing the informed consent and during the follow-up period, including laboratory test abnormalities fulfilling the definition of SAE, whether or not considered related to the study medications or procedures, will be recorded on the Serious Adverse Event form and forwarded to the study PI as soon as possible. The PI or designee will forward the reports to appropriate authorities (DSM, FDA, NHLBI, Pharmaceutical supplier) according to the institutional guidelines. All adverse events will also we reported to the IRB according to the institutional AE reporting guidelines. Every attempt will be made to collect discharge summaries for each hospitalization to provide further details.

Collect Unused Study Drug: Unused drug will be collected and Visits 4 and 5; upon completion of the study, unused study drug will be collected and destroyed.

6.2.1 Screening Evaluation

Adults 18 and older, with physician diagnosed mild to severe persistent asthma will be screened. After reviewing and signing informed consent, subjects that fulfill inclusion and exclusion criteria will be invited to participate.

Consenting Procedure

Single informed consent describing screening and study procedures.

The study PI (Emily DiMango, MD) or the research study coordinator (Amanda Kramer) will conduct the consent process.

Emily DiMango is a professor of medicine and pulmonologist and director of the John Edsall-John Wood Asthma Center at Columbia University Medical Center. Amanda Kramer, B.S. has over 3 years of experience as a clinical research coordinator and has experience consenting and studying pulmonary

patients during clinical studies in the John Edsall-John Wood Asthma Center.

Any changes in the consent form will only occur after approval from the institutional IRB and the NCCIH.

Documentation of the consent process and consent forms will be retained in a research study binder.

Screening

Visit 1: Screening Visit

Sequence of events:

- Identify patients that are adults 18 and older with physician-diagnosed mild to severe persistent asthma
- Sign informed consent
- Fulfill inclusion and exclusion criteria
- Review of medical history
- Record Demographics
- Recording of medication use
- Physical exam including vital signs by study MD or NP
- Urine pregnancy test for women of child bearing age
- Scoring on ACT ≤ 19
- Scoring on basic spirometry before and after bronchodilator

Required to be eligible:

- Patients that are adults 18 and older with physician-diagnosed mild to severe persistent asthma
- Signing informed consent
- Fulfill inclusion and exclusion criteria
- Using inhaled corticosteroids with or without inhaled long acting beta agonists or anti-muscarinics.
- Scoring on ACT ≤ 19
- Negative urine pregnancy test for women of child bearing age

Screening must be completed 14-21 days prior to visit 2 during which the ACT score will be confirmed to be ≤ 19, and the baseline FEV1 is ≥ 60% of predicted (or 1.5L); Baseline methacholine PD20 will be determined at V2 as a subsequent eligibility criterion.

Visit 2; Day 14 to 21:

- Administer ACT. If ACT remains ≤19, proceed . If ACT > 19 consistent with good asthma control, terminate from study.
- Confirm medication washouts (reschedule if not met).
- Spirometry
- methacholine bronchoprovocation testing if FEV1 is ≥ 60% or 1.5L (reschedule or terminate if < 60% or 1.5L) to assess baseline methacholine PD20.
- Administer BD for Methacholine Recovery Challenge

6.2.2 Enrollment, Baseline, and/or Randomization

Enrollment

A single informed consent form will be used for screening and enrollment. The enrollment date will be defined as the date that all of the screening criteria are met and the individual agrees to participate.

The enrollment date will be recorded on the case report form and the allowable window from enrollment to randomization will be 15-22 days.

Baseline Assessments

- Baseline FEV1
- Baseline methacholine PD20
- Baseline ACT score

● Baseline QOL and Asthma 2 week recall questionnaires
● Baseline GI symptoms
● Baseline Exhaled Nitric Oxide
● Blood draw for eosinophils, cytokines, biomarkers
● Blood draw for metabolite measurements in subjects participating in PK study

Randomization

Randomization to initiation of study intervention will occur on the same day. Randomization will occur at visit 3 and will precede an intervention (i.e. starting of oral ginger or placebo).
Randomization is a process that assigns participants/subjects by chance (rather than by choice) into specific groups, typically for clinical research and clinical trials. An independent statistican will generate the randomization codes and allocations. The blinded study coordinator will retrieve the randomization allocation through RedCap. RedCap is an institutionally available automated system for randomization and the independent statistician will have direct oversight over the process. The blinded study team will not have access to the randomization codes. In this module, randomization model is defined as Drug A and Drug B in a 1:1 ratio. Drug A and Drug B may refer to placebo or active drug, however they are left coded as such to ensure blinding. The module creates a template allocation table, which the user uses to structure the randomization table to be imported. The module also monitors the overall allocation progress and assignment of randomized subjects to ensure balanced proportions of active drug and placebo. Only one site member will be allowed randomization priviledges, but the site will confirm, and lock the specific data field to ensure that no data is altered after randomization. There is no stratification, and there are no variable block sizes..

6.2.3 Blinding

Ginger extract and placebo capsules have been pre-packaged and labeled with a code by the distributor (Atrium Innovations, Pure Encapsulations) and delivered to the research pharmacy at the Columbia University Medical Center. We do not anticipate any collected data offering evidence of a participant's assignment to a particular arm. All study data is collected objectively without an opportunity for the collected data to identify the study arm. For example, changes in methacholine PD20 and exhaled nitric oxide (primary outcomes) will vary over the course of the study in both ginger and placebo treated subjects. These variations will not be able to offer evidence of group membership and will only be informative after analysis in the aggregate.

The study PIs, Emily DiMango, MD, Charles Emala, MD are authorized to break the blind if there is a concern for subject safety, a serious adverse event or safety concerns raised by the DSMB. The PIs will contact the independent statistician who will be holding the codes. The PIs, Research Coordinator, study statistician(s), subjects and research pharmacy will be blinded. The research pharmacy will be notified as to randomization to drug A or B but will be unaware of which is ginger versus placebo.

6.2.4 Followup Visits

Visit 3 Day 15-22 RANDOMIZATION VISIT
Procedures Performed:

- Administer questionnaires (ACT, QOL, A2WR)
- Review medical history, conmeds, and AEs since the screening visit
- Confirm medication washouts (reschedule if not met)
- Vitals
- Urine Pregnancy Test (if applicable)
- Physical Exam
- Review Randomization Inclusion/Exclusion Criteria
- Baseline GI side effect check list
- Randomize
- Measure Exhale Nitric Oxide (FeNO)

- Pre-dose Spirometry
- Blood draw cytokines, biomarkers and blood eosinophil count
- Pre-dose Pharmacokinetic blood draw for select subjects
- Administer 1st dose of study drug
- Post-Dose Spirometry (1 hr post-study drug dosing)
- Pharmacokinetic blood draw for select subjects (n =8 4 Males & 4 Females) (Time 0.5, 1, 2, 3, 4 & 8 hrs)- **PK Subgroup only.**
- Dispense drug

Visit 3A Day 29-36: Phone contact to answer questions and encourage compliance.

Visit 4 Day 43-50 (Day 28 of study drug):
Procedures Performed:

- Administer questionnaires (ACT, QOL, A2WR)
- Review conmeds, and AEs since V3
- Review study drug compliance (pill count)
- Confirm medication washouts (reschedule if not met)
- GI side effect checklist
- Vitals
- Urine Pregnancy Test (if applicable)
- Physical Exam
- Exhale Nitric Oxide (FeNO)
- Spirometry
- Perform Methacholine Challenge --- reschedule visit if FEV1 is < 60% or 1.5L
- Administer bronchodilator
- Methacholine Recovery Challenge
- Blood draw cytokines, biomarkers and blood eosinophil count
- Pre-dose Pharmacokinetic blood draw--**PK subgroup only.**
- Study Drug Dosing
- Pharmacokinetic blood draw (Time 0.5, 1, 2, 3, 4 & 8 hrs)—**PK subgroup only.**

Visit 4A Day 44-70: Phone or email contact to answer questions and encourage compliance.

Visit 5 Day 71-78 (Day 56 of study drug)
Procedures Performed:

- Administer questionnaires (ACT, QOL, A2WR)
- Review conmeds, and AEs since the previous visit (V4)
- Review study drug compliance (pill count)
- Confirm medication washouts (reschedule if not met).
- GI side effect check list
- Vitals
- Urine Pregnancy Test (if applicable)
- Physical Exam
- Exhale Nitric Oxide (FeNO)
- Spirometry
- Perform Methacholine Challenge --- reschedule visit if FEV1 is < 60% or 1.5 L
- Administer bronchodilator
- Methacholine Recovery Challenge
- Collect Blood for cytokines, biomarkers and eosinophil count
- Pre-dose Pharmacokinetic blood draw--**PK subgroup only.**
- Study Drug Dosing for PK group only
- Pharmacokinetic blood draw (Time 0.5, 1, 2, 3, 4 & 8 hrs)—**PK subgroup only.**
- Collect unused study drug.

6.2.5 Completion/Final Evaluation

Visit 5 Day 71-78 (Day 56 of study drug)
Procedures Performed:

- Administer questionnaires (ACT, QOL, A2WR)
- Review conmeds, and AEs since the previous visit (V4)
- Review study drug compliance (pill count)
- Confirm medication washouts (reschedule if not met).
- GI side effect check list
- Vitals
- Urine Pregnancy Test (if applicable)
- Physical Exam
- Exhale Nitric Oxide (FeNO)
- Spirometry
- Perform Methacholine Challenge --- reschedule visit if FEV1 is < 60% or 1.5 L
- Administer bronchodilator
- Methacholine Recovery Challenge
- Collect Blood for cytokines, biomarkers and eosinophil count
- Pre-dose Pharmacokinetic blood draw--**PK subgroup only.**
- Study Drug Dosing
- Pharmacokinetic blood draw (Time 0.5, 1, 2, 3, 4 & 8 hrs)—**PK subgroup only.**
- Collect study drug.

Any subjects who discontinue the study early will be contacted to determine the reason why. These reasons will be documented in the study binder. If termination occurs to lack of tolerance or adverse events related to the study drug or procedures, protocols for reporting adverse events will be followed as outlined below.

7. SAFETY ASSESSMENTS

Bronchodilator: (albuterol/salbuterol) will be available to be administered if the participant is uncomfortable from the effects of the methacholine challenge test, and also be used for reversibility testing after spirometry at V1. These drugs can lead to tremor, nervousness, tachycardia, palpitations and headache – these reactions are transient and rare (<5%) with the proposed doses used for this study, and if they occur, we will monitor the patient until they return to baseline. High doses may cause arrhythmias and hypokalemia: these are very unlikely with the doses used for this study.

Exhaled NO (FeNO): Exhaled breath will be collected from forced expirations using disposable mouthpieces for the online exhaled NO (Circassia) procedure described in the American Thoracic Society (ATS) guidelines. There are no known risks involved with breathing into the collection system.

GI side effects: Patients will be asked about the frequency and severity of GI symptoms including eructation, heartburn, nausea, bloating or indigestion.

Methacholine challenge: involves the inhalation of an agonist to induce bronchoconstriction and may induce the symptoms of an asthma exacerbation (chest tightness, dyspnea, coughing). The procedure is performed in a closely monitored clinical environment, with availability of bronchodilator. This procedure has been safely used in many previous studies by our group; we will only perform this procedure if the baseline FEV_1 is > 60% predicted.

Questionnaires and assessments*:* Participants will be asked to provide information about their psychological, physical, and medical functioning on questionnaires.

Asthma Control Test (ACT). The self-administered validated ACT will be used for this measurement.

Juniper mini-Asthma specific quality of life (mini AQOL). Disease specific quality of life will be measured via the Juniper mini-Asthma Quality of Life questionnaire, a validated questionnaire.

2 week recall questionnaire: The Asthma two week recall (A2WR) was developed to capture the inherent intensity of the disease in individuals with asthma. It quantifies severity by combining information about impairment, risk, and the amount of medication required to maintain control.

Pulmonary Function Testing: requires deep and forceful respiratory efforts. It is a commonly performed and safe examination that is widely performed in patients with lung disorders. Some patients report chest soreness the day following the procedure. Some patients may experience light-headedness during the forced expiration. The risk of syncope is mitigated by having the patient perform the test in the seated rather than standing position.

Venous Blood Draw: For each blood draw, approximately 10 ml of venous blood will be drawn by phlebotomy from an upper extremity. For patients who consent to the pharmacokinetics study, an additional 105 ml of blood will be required. Blood drawing may cause a small amount of pain. In addition, a temporary bruise may develop. Rarely, people faint after blood drawing. Very rarely, the vein in which the needle has been inserted may become inflamed or infected.

Ginger is widely used as an over-the-counter dietary supplement. The formulation and amount of ginger used in this study (**2g per day**; Pure Encapsulations®) has been chemically characterized by HPLC and has been administered to patients at the oral amount (2 grams) for 28 days in multiple human studies measuring inflammatory mediators in colonic mucosal biopsies. The incidence of side effects in a 28 day trials of 30 individuals were not significantly different in placebo versus ginger and no adverse events were greater than the NCI Common Toxicity Criteria Grade 1. In a second study of 27 individuals no adverse event greater than NCI Common Toxicity Criteria Grade 1 was reported (no placebo comparison) and the leading complaints were gastrointestinal symptoms of eructation, heartburn or indigestion.[7] In a third study of 20 patients consuming the same formulation in the same amount for the same duration (2g, Pure Formulations, 28 days) no statistically significant increase in adverse events occurred compared to placebo, no toxicities were greater than the NCI Common Toxicity Criteria Grade 1 and included bloating, nausea and heartburn.[16]

There have been small numbers of studies reporting on possible inhibition of platelet aggregation by ginger. Ginger has been shown an in vitro study to inhibit platelet aggregation with a potency similar to that of aspirin and in another study of human volunteers, to have a syngergistic effect with nifedipine in platelet aggregation.[8-10] A single case report has been published demonstrating epistaxis in a women who was being treated with Coumadin who subsequently started taking ginger.[11] Subjects taking anti-coagulation will be excluded from participation, though subjects taking aspirin alone will be included in the study since there have been no studies or reports of increased bleeding risk with aspirin and ginger combined.

7.1 Specification of Safety Parameters

- ***Methacholine challenge*** involves the inhalation of an agonist to induce bronchoconstriction and may induce the symptoms of an asthma exacerbation (chest tightness, dyspnea, coughing). The procedure is performed in a closely monitored clinical environment, with availability of bronchodilator. This procedure has been safely used in many previous studies by our group; we will only perform this procedure if the baseline FEV_1 is > 60% predicted.
- ***Bronchodilator*** (albuterol/salbuterol) will be available to be administered if the participant is uncomfortable from the effects of the methacholine challenge test.
- ***GI side effects*** will assessed at each study visit.
- ***Venous Blood Draw***: Rarely, people faint after blood drawing and therefore will be seated during blood draws. Very rarely, the vein in which the needle has been inserted may become inflamed or infected.

7.2 Methods and Timing for Assessing, Recording, and Analyzing Safety Parameters

●***Pulmonary function testing***: (spirometry or methacholine provocation) adverse effects are immediately apparent during the test and will be treated (albuterol inhaler) and recorded in the case report forms.

●***GI side effects:***[7,16] This will be assessed at each study visit to ensure tolerance of the ginger capsules and will be recorded in the case report forms. Evidence of GI intolerance will be addressed as detailed in adverse events below.

●**Venous Blood Draw***:* Rare fainting during blood draws occurs due to a vaso-vagal response and is immediately apparent. Subjects will have their blood pressure and heart rate assessed and will be monitored until they return to normal. Very rarely, the vein in which the needle has been inserted may become inflamed or infected. Blood draw sites will be inspected at each clinic visit.

7.3 Adverse Events and Serious Adverse Events

An Adverse Event (AE) is any unfavorable and unintended symptom, or disease temporally associated with the administration of ginger or the clinical testing proposed that may or may not be considered related to the medical treatment or procedure. Adverse events will be recorded regardless of their relationship to the study intervention.
Defining: A serious adverse event (SAE) is one that meets one or more of the following criteria:

- Results in death
- Is life-threatening (places the subject at immediate risk of death from the event as it occurred)
- Results in inpatient hospitalization or prolongation of existing hospitalization
- Results in a persistent or significant disability or incapacity
- Results in a congenital anomaly or birth defect

An important medical event that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Adverse Event solicited and unsolicited:
Solicited at each study visit:

●Gastrointestinal side effects (including eructation, heartburn, nausea, bloating or indigestion)
●Venipuncture complications (swelling, infection)

Unsolicited at each study visit:

●Patients will have a general medical examination and vital signs at every visit.

7.4 Reporting Procedures

Reporting: SAEs that are unanticipated, serious, and possibly related to the study intervention will be reported to the Independent Monitors(s), IRB, FDA, and NCCIH in accordance with requirements. To satisfy the requirement for prompt reporting, unanticipated problems will be reported using the following timeline:

- Unanticipated problems that are serious adverse events will be reported to the IRB within 48 hours and to the Independent Safety Monitor(s) and to the NCCIH within 7 days of the investigator becoming aware of the event.
- Any other unanticipated problem will be reported to the IRB, Independent Safety Monitor(s), and NCCIH within 14 days of the investigator becoming aware of the problem.

All unanticipated problems should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and OHRP within one month of the IRB's receipt of the report of the problem from the investigator.
Reporting to the FDA for the IND:

- 7-day IND Safety Report (unexpected fatal or life-threatening AEs related to the intervention); a copy of the report sent to the FDA will be submitted to the NCCIH Program Officer and Independent Safety Monitor(s) within 24 hours of FDA notification.
- 15-day IND Safety Report (any other serious and unexpected AE related to the intervention); a copy of the report submitted to the FDA will be submitted to the NCCIH Program Officer and Independent Safety Monitor(s) within 24 hours of FDA notification.
- All other AEs documented during the course of the trial will be reported to NCCIH on an annual basis by way of inclusion in the annual report and in the annual AE summary which will be provided to NCCIH and to the Independent Monitors. The Independent Safety Monitor(s) Report will state that all AEs have been reviewed.

7.5 Followup for Adverse Events

Subjects will be followed up as outpatients for adverse events that are not serious adverse events. Subjects will be followed up until symptoms of adverse events resolve. For serious adverse events, subjects will be followed up as an inpatient or outpatient as deemed appropriate by the treating physician. The follow up will continue until the adverse event is resolved or stabilized.

7.6 Safety Monitoring

Dr. Jeanine D'Armiento, a pulmonologist, and Dr. Caleb Ing, a physician and epidemiologist, will serve as the data and safety monitors for the proposed study.

8. INTERVENTION DISCONTINUATION

Adverse gastrointestinal events associated with the consumption of ginger that require medical intervention (intravenous fluid administration, hospital admission) will prompt temporary suspension of enrollment and/or study interventions until a complete safety review is convened. Adverse reactions to inhaled methacholine that require hospital admission will prompt temporary suspension of enrollment and/or study interventions until a complete safety review is convened. Subsequent review of serious, unexpected, and related AEs by the DSMB, Independent Safety Monitor(s), IRB or the FDA may also result in suspension of further study interventions/administration of study product. The FDA retain the authority to suspend additional enrollment and study interventions/administration of study product for the entire study, as applicable.

Participants will continue to be followed with their permission if study intervention is discontinued. Temporary discontinuation of treatment would interrupt the consecutive 56 day treatment plan and thus subjects would be removed from the study. If a subject is removed from the study, evaluations related to any adverse events would be continued as defined in section 7.5 above.

9. STATISTICAL CONSIDERATIONS

9.1 General Design Issues

We hypothesize that the oral consumption of Pure Encapsulation® ginger extract (2g/day by adult patients with moderate to severe asthma despite normal maintenance medications, will have an improvement in their tolerance to inhaled methacholine or a reduction in lung inflammation over the 56 day treatment period.

This is a randomized, double blind, placebo-controlled design. Patients will have baseline measurements of their pulmonary function and inflammation status and will then be randomized to ginger extract or placebo. The same measurements of pulmonary function and inflammation status will be repeated at 28 and 56 days of ginger or placebo consumption. The durations of 28 and 56 days were chosen because it is hypothesized that the primary benefit of consumption of oral ginger will be an anti-inflammatory effect in

the lung that over time results in improved pulmonary function.

Primary hypotheses: are that the oral daily consumption of ginger will improve the tolerance to inhaled methacholine and/or a reduction in exhaled nitric oxide.

Secondary hypotheses: are that an additional measure of pulmonary function will improve (an increase in baseline FEV1) and/or that secondary measures of inflammation (eosinophilia, asthma associated cytokines) will improve.

Primary outcome measures: The primary outcome measures are methacholine (PD20) and exhaled nitric oxide. These outcomes will be measured at visit 3 (baseline) and visits 4 and 5 (days 28 and 56 of the oral ginger or placebo consumption).

Secondary outcome measures: A clinically significant increase in baseline FEV1 of 100ml. For subjects with eosinophilia (>300 cells/ul) a 32% decrease in blood eosinophils[17], a 40% decrease in serum IL4[18,19], a 50% decrease in serum IL5[20] or a 75% decrease in serum IL13.[21]

9.2 Sample Size and Randomization

We utilized published literature to identify the magnitude of change in our primary outcomes that are clinically relevant. As illustrated in the table in section 3, we calculated a need of 14 subjects per arm for the methacholine measurement and 16 subjects per arm for the exhaled nitric oxide assessment (same subjects studied in methacholine and exhaled nitric oxide assays). Thus we need 16 subjects per arm and anticipate a 10% attrition rate overall requiring 36 subjects. As illustrated in the table in section 3, an enhanced tolerance to inhaled methacholine of 0.7X the doubling dose is considered clinically significant.[12] We anticipate a S.D. of 0.6 in both groups and aim to achieve 80% power at the 0.05 significance level. This requires 14 subjects for each of the two arms. For exhaled nitric oxide with baselines starting at >50ppb, a 20% decrease is considered clinically significant. We expect a S.D. of ~ 37 and aim to achieve 80% power at the 0.05 level and will thus require 16 subjects for each of two arms.

Treatment Assignment Procedures

Subjects will be randomized to treatment A or B in a blinded fashion using the randomization algorithm within REDCap. The randomization module in REDCap implements a defined randomization model within the project, allowing the site to randomize the subjects. In this module, randomization model is defined as Drug A and Drug B in a 1:1 ratio. Drug A and Drug B may refer to placebo or active drug, however they are left coded as such to ensure blinding. The module creates a template allocation table, which the user uses to structure the randomization table to be imported. The module also monitors the overall allocation progress and assignment of randomized subjects to ensure balanced proportions of active drug and placebo. Only one site member will be allowed randomization priviledges, but the site will confirm, and lock the specific data field to ensure that no data is altered after randomization. There is no stratification, and there are no variable block sizes.

Trial randomization codes for each individual subject will be retained within the REDCap data set as treatment A or B. The independent statistician retains the identity of A or B and does not disclose this to the study conductors. The planned breaking of the code will occur after data analysis is complete. Unplanned breaking of the code will occur if a medical condition mandates such an action.

Ginger extract and placebo capsules have been pre-packaged and labeled with a code by the distributor (Atrium Innovations, Pure Encapsulations) and delivered to the research pharmacy at the Columbia University Medical Center. We do not anticipate any collected data offering evidence of a participant's assignment to a particular arm. All study data is collected objectively without an opportunity for the collected data to identify the study arm. For example, changes in methacholine PD20 and exhaled nitric oxide (primary outcomes) will vary over the course of the study in both ginger and placebo treated subjects. These variations will not be able to offer evidence of group membership and will only be informative after analysis in the aggregate.

The study PIs, Emily DiMango, MD, Charles Emala, MD are authorized to break the blind if there is a concern for subject safety, a serious adverse event or safety concerns raised by the DSMB. The PIs will contact the research pharmacy who will be holding the codes.

No stratification of the randomization will occur.

9.3 Definition of Populations

Adults aged 18 years and above, with mild to severe persistent asthma will be enrolled. Subjects will have asthma which is not optimally controlled despite the current use of inhaled corticosteroids with or without inhaled long-acting beta agonists. The populations will be those subjects randomized to the placebo arm versus ginger extract arm.

All randomized subjects will be included in the primary analysis, analyzed based on intention-to-treat. In addition, a secondary analysis based on per protocol will be conducted. Per protocol analysis will exclude patients who missed 30% or more of their assigned treatment. Please refer to section 5.4 for the equation to calculate compliance.

9.4 Interim Analyses and Stopping Rules

No interim analysis is planned. Due to the extensive use of this same formulation of ginger extract in the same daily dose, we expect no safety concerns and excellent tolerance. We have greatly exceeded these enrollment numbers in numerous previous asthma clinical studies in the John Edsall-John Wood Asthma Center at Columbia University Medical Center and believe that it is highly unlikely that this study will demonstrate poor study performance.

Adverse gastrointestinal events associated with the consumption of ginger that require medical intervention (intravenous fluid administration, hospital admission) will prompt temporary suspension of enrollment and/or study interventions until a complete safety review is convened. Adverse reactions to inhaled methacholine that require hospital admission will prompt temporary suspension of enrollment and/or study interventions until a complete safety review is convened. Subsequent review of serious, unexpected, and related AEs by the DSMB, Independent Safety Monitor(s), IRB or the FDA may also result in suspension of further study interventions/administration of study product. The FDA retain the authority to suspend additional enrollment and study interventions/administration of study product for the entire study, as applicable.

9.5 Outcomes

Outcomes will be analyzed when all patients have completed the study at day 56 by both PIs and the statistical consultant on this study (Shuang Wang, PhD) who will be blinded from the study group until the data analysis is completed.

9.5.1 Primary Outcome

The primary outcomes are a clinically significant change in tolerance to inhaled methacholine (PD20) or a clinically significant change in exhaled nitric oxide. These outcomes will be measured at visit 3 (baseline) and visits 4 and 5 (days 28 and 56 of the oral ginger or placebo consumption).

9.5.2 Secondary Outcomes

Secondary outcome measures: A clinically significant increase in baseline FEV1 of 100ml. For subjects with eosinophilia (>300 cells/ul) a 32% decrease in blood eosinophils15, a 40% decrease in serum IL416,17, a 50% decrease in serum IL518 or a 75% decrease in serum IL13.19

9.6 Data Analyses

We will compare the change in log-transformed methacholine reactivity (PD20) in the ginger versus the placebo group using two-sample t-test. We will compare patients' initial PD_{20} (day 0) to their subsequent PD_{20} at days 28, 56 using paired t-test. It is possible that the PD_{20} measurements on days 0, 28 and 56 could be influenced by the consumption of oral ginger 1 hour prior so we will also compare the PD_{20} at

day 0 to those at 28 and 56. An acute benefit in methacholine tolerance will be reflected in a significant improvement between PD_{20}'s at days 0, 28 and 56 while a chronic improvement will be reflected in improved PD_{20}'s at days 28 and 56 compared to day 0.

Patients with asthma have remarkably consistent fractional exhaled nitric oxide (FeNO) levels when measured over time with mild-moderate asthmatics having FeNO values of approximately 40 ± 10 ppb.[22] We will consider a 25% change in FeNO as biologically significant[23] comparing each patient's initial FeNO to their subsequent FeNO at days 28, 56 using paired t-test.

Data from prior studies does not support the existence of significant differences in the intervention effect between subgroups and thus subgroup analysis will not be performed.

10. DATA COLLECTION AND QUALITY ASSURANCE

10.1 Data Collection Forms

Information for each participant will be collected by the lead study clinical coordinator (Amanda Kramer) and the PIs (Emily DiMango, MD and Charles Emala, MD) and recorded on case report forms (please see attachments under appendices, section 15 of this document) that will be electronically recorded within REDCap. All 3 of these individuals will be blinded as to the study group of the subject.

10.2 Data Management

Access to clinical data will be limited to the clinical study coordinator, Dr. DiMango and Dr. Emala. All data will be stored within REDCap via desktop computers that are encrypted, password protected and physically located on the Columbia University campus. All participants will be assigned a unique non-identifying number for which all their data and blood samples will be labeled. The key for this list will only be retained by the 3 individuals and devices named above. No personal identifying information will be available outside of this coded list on these protected devices.

Data from this single site study will be stored within REDCap.

The case report forms for each study visit are attached in the appendicies, section 15 of this document.

10.3 Quality Assurance

10.3.1 Training

All individuals involved in this study have completed all institutional and IRB-required training for participation in human clinical trials including but not limited to GCP and HIPPA training. The study coordinator has been trained in the administration of spirometry, methacholine provocation testing, administration of bronchodilators and phlebotomy. All of these procedures will occur in a monitored clinical setting (the John Edsall-John Wood Asthma Center at Columbia University Medical Center).

10.3.2 Quality Control Committee

The PIs (Drs. DiMango and Emala) and study coordinator (Amanda Kramer) will meet monthly to review case report forms and study binders.

10.3.3 Metrics

Spirometry: Subjects will be asked to perform pulmonary function testing for collection of lung function data at each visit. Pulmonary function testing will be performed according to American Thoracic Society (ATS) guidelines (2005). Subjects will be tested using the same spirometry equipment at every visit. Up to 8 efforts will be performed to obtain 3 acceptable and reproducible test results. The best results from the 3 acceptable and reproducible efforts for PFTs will be recorded on the subject's case report form and a copy of the spirometry reports will be retained with the subject's source documents.
Methacholine provocation: The spirometer will be calibrated daily as per ATS guidelines.

10.3.4 Protocol Deviations

Protocol deviations will be captured during subject visits. This will occur by questioning of concurrent medications, appropriate washout of asthma-related medications, pill counts and 2 week recall questionnaires. We will also include less than 70% study drug compliance as a protocol deviation. These will be documented on case report forms. Some deviations (e.g. failure to abide by washout criteria) will result in rescheduling of study visits until the washout period is achieved. Deviations will be review monthly during scheduled meetings of Drs. DiMango, Emala and the research coordinator. Significant deviations (e.g. failure to comply with consumption of ginger or placebo capsules, failure to appear for study visits within the allowed windows) will result in subject removal from the study.

10.3.5 Monitoring

Data type	Frequency of review	Reviewer
Subject accrual (including compliance with protocol enrollment criteria)	Monthly	PIs & research study coordinator(s)
	Semi-annually	Independent Monitors Caleb Ing, MD & Jeanine D'Armiento, MD, PhD
Status of all enrolled subjects, as of date of reporting	Monthly	PIs & research study coordinator(s)
	Semi-annually	Independent Monitors Caleb Ing, MD & Jeanine D'Armiento, MD, PhD
Data entry quality control checks on 5% of charts	Quarterly	Claire Goelst (departmental clinical compliance coordinator)
Adherence data regarding study visits and intervention	Monthly	PIs & research study coordinator(s)
Adherence data regarding study visits and intervention AEs and rates (including out-of-range lab values)	Semi-annually	Independent Monitors Caleb Ing, MD & Jeanine D'Armiento, MD, PhD
	Monthly	PIs & research study coordinator(s)
AEs and rates (including out-of-range lab values) SAEs (unexpected and related)	Semi-annually	Independent Monitors Caleb Ing, MD & Jeanine D'Armiento, MD, PhD
	Annually	NCCIH, FDA (If Applicable)
	Per occurrence	PIs & Independent Monitors Caleb Ing, MD & Jeanine D'Armiento, MD, PhD NIH/NCCIH, FDA (if applicable)
SAEs (expected or unrelated)	Per Occurrence	PIs &Claire Goelst (departmental clinical compliance coordinator)
SAEs (expected or unrelated) Unanticipated Problems	Annually	Independent Monitors Caleb Ing, MD & Jeanine D'Armiento, MD, PhD NIH/NCCIH

	Monthly	PIs & research study coordinator(s)
Unanticipated Problems	Per Occurrence	IRB, FDA (if applicable)

11. PARTICIPANT RIGHTS AND CONFIDENTIALITY

11.1 Institutional Review Board (IRB) Review

This protocol and the informed consent document and any subsequent modifications will be reviewed and approved by the IRB for oversight of the study. The consent form is separate from the protocol document.

11.2 Informed Consent Forms

A signed consent form will be obtained from each participant. Consent forms are available in the English and Spanish language. The consent form describes the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy will be given to each participant and this fact will be documented in the participant's record.

11.3 Participant Confidentiality

Participant data, which includes identifiable personal health information (PHI), will be collected at the clinical site. PHI will be stored in accordance with HIPAA regulations and local university and hospital policies. This includes the storage of PHI in locked cabinets or rooms, limited access to secure data areas by certified study personnel, password protection for electronic medical records, and explanation of HIPAA regulations on the study consent form. Analytic files will not contain personal identifiers (e.g. name, address). Reports/manuscripts will be prepared in such a way that individual participants cannot be identifiable.

Data such as lung function or laboratory tests that are collected as part of this study may be transmitted to the participants treating physicians with the consent of the participant. Participants will be informed in the consent that PHI may also be disclosed for auditing purposes by the NIH or other regulatory bodies and is subject to subpoena.

Personal identifiers (e.g. name, address, EMR number) are not transmitted to the Data and Safety Monitor or central laboratory in that all biospecimens and records are identified by a study ID, and other identifying information such as names are not entered into the central study database. Source records that are transmitted to the Data and Safety monitor for data quality audits have identifying information redacted. No highly confidential information is routinely collected, although the data collection does include PHI, so a breach of confidentiality would constitute a HIPAA violation.

We will advise participants that the U.S. Department of Health and Human Services has the right to inspect medical records relating to this research for the purposes of verifying data. Where data are shared with other research entities, it will comply with the HIPAA definition of a limited dataset, and appropriate IRB approvals and waivers will be obtained.

11.4 Study Discontinuation

The study may be discontinued at any time by the IRB, the NCCIH, the OHRP, the FDA, or other government agencies as part of their duties to ensure that research participants are protected.

12. COMMITTEES

The PIs (Emily DiMango,MD and Charles Emala,MD) will be responsible for the overall conduct of the study, data management, data analysis, publications and reports to respective committees (IRB, FDA, NCCIH, DSMB).

A Data Safety Monitoring Board consisting of two individuals not affiliated with the study and without

conflicts of interest with the PIs will meet with the PIs semi-annually or per occurrence for adverse events to review documents as detailed in the table above in section 10.3.5.

13. PUBLICATION OF RESEARCH FINDINGS

Any presentation, abstract, or manuscript will be made available for review by the NCCIH prior to submission.

14. REFERENCES

1. National Heart L, Blood Institute: National Asthma Education and Prevention Program; Expert Panel Reprot 3:Guidelines for the Diagnosis and Management of Asthma. 2007: 74
2. Sondik EM, J.;Gentleman,J.: Summary Health Statistics for U.S. Adults: National Health Interview Survey 2011. Edited by Services USDoHaH. Vital and Health Statistics edition, Center for Disease Prevention and Control, 2012, pp 1-218
3. Jobin MS, Moisan J, Bolduc Y, Dorval E, Boulet LP, Gregoire JP: Factors associated with the appropriate use of asthma drugs. Can Respir J 2011; 18: 97-104
4. Singh BB, Khorsan R, Vinjamury SP, Der-Martirosian C, Kizhakkeveettil A, Anderson TM: Herbal treatments of asthma: a systematic review. J Asthma 2007; 44: 685-98
5. Mali RG, Dhake AS: A review on herbal antiasthmatics. Orient Pharm Exp Med 2011; 11: 77-90
6. Townsend EA, Siviski ME, Zhang Y, Xu C, Hoonjan B, Emala CW: Effects of ginger and its constituents on airway smooth muscle relaxation and calcium regulation. Am J Respir Cell Mol Biol 2013; 48: 157-63
7. Zick SM, Turgeon DK, Vareed SK, Ruffin MT, Litzinger AJ, Wright BD, Alrawi S, Normolle DP, Djuric Z, Brenner DE: Phase II study of the effects of ginger root extract on eicosanoids in colon mucosa in people at normal risk for colorectal cancer. Cancer Prev Res (Phila) 2011; 4: 1929-37
8. Koo KL, Ammit AJ, Tran VH, Duke CC, Roufogalis BD: Gingerols and related analogues inhibit arachidonic acid-induced human platelet serotonin release and aggregation. Thromb Res 2001; 103: 387-97
9. Nurtjahja-Tjendraputra E, Ammit AJ, Roufogalis BD, Tran VH, Duke CC: Effective anti-platelet and COX-1 enzyme inhibitors from pungent constituents of ginger. Thromb Res 2003; 111: 259-65
10. Young HY, Liao JC, Chang YS, Luo YL, Lu MC, Peng WH: Synergistic effect of ginger and nifedipine on human platelet aggregation: a study in hypertensive patients and normal volunteers. Am J Chin Med 2006; 34: 545-51
11. Kruth P, Brosi E, Fux R, Morike K, Gleiter CH: Ginger-associated overanticoagulation by phenprocoumon. Ann Pharmacother 2004; 38: 257-60
12. Cahill KN, Katz HR, Cui J, Lai J, Kazani S, Crosby-Thompson A, Garofalo D, Castro M, Jarjour N, DiMango E, Erzurum S, Trevor JL, Shenoy K, Chinchilli VM, Wechsler ME, Laidlaw TM, Boyce JA, Israel E: KIT Inhibition by Imatinib in Patients with Severe Refractory Asthma. N Engl J Med 2017; 376: 1911-1920
13. Dweik RA, Boggs PB, Erzurum SC, Irvin CG, Leigh MW, Lundberg JO, Olin AC, Plummer AL, Taylor DR, American Thoracic Society Committee on Interpretation of Exhaled Nitric Oxide Levels for Clinical A: An official ATS clinical practice guideline: interpretation of exhaled nitric oxide levels (FENO) for clinical applications. Am J Respir Crit Care Med 2011; 184: 602-15
14. Pasha MA, Smith TC, Feustel PJ, Jourd'heuil D: Effects of low-dose fluticasone propionate/salmeterol combination therapy on exhaled nitric oxide and nitrite/nitrate in breath condensates from patients with mild persistent asthma. J Asthma 2013; 50: 64-70
15. Zick SM, Ruffin MT, Lee J, Normolle DP, Siden R, Alrawi S, Brenner DE: Phase II trial of encapsulated ginger as a treatment for chemotherapy-induced nausea and vomiting. Support Care Cancer 2009; 17: 563-72
16. Zick SM, Turgeon DK, Ren J, Ruffin MT, Wright BD, Sen A, Djuric Z, Brenner DE: Pilot clinical study of the effects of ginger root extract on eicosanoids in colonic mucosa of subjects at increased risk for colorectal cancer. Mol Carcinog 2014
17. Leckie MJ, ten Brinke A, Khan J, Diamant Z, O'Connor BJ, Walls CM, Mathur AK, Cowley HC, Chung KF, Djukanovic R, Hansel TT, Holgate ST, Sterk PJ, Barnes PJ: Effects of an interleukin-5

blocking monoclonal antibody on eosinophils, airway hyper-responsiveness, and the late asthmatic response. Lancet 2000; 356: 2144-8
18. Lama M, Chatterjee M, Nayak CR, Chaudhuri TK: Increased interleukin-4 and decreased interferon-gamma levels in serum of children with asthma. Cytokine 2011; 55: 335-8
19. Cui AH, Zhao J, Liu SX, Hao YS: Associations of IL-4, IL-6, and IL-12 levels in peripheral blood with lung function, cellular immune function, and quality of life in children with moderate-to-severe asthma. Medicine (Baltimore) 2017; 96: e6265
20. Kato M, Yamada Y, Maruyama K, Hayashi Y: Differential effects of corticosteroids on serum eosinophil cationic protein and cytokine production in rhinovirus- and respiratory syncytial virus-induced acute exacerbation of childhood asthma. Int Arch Allergy Immunol 2011; 155 Suppl 1: 77-84
21. Janeva EJ, Goseva Z, Gjorchev A, Debreslioska A, Spiroski M, Zafirova B, Dimitrova MG: The Effect of Combined Therapy ICS/LABA and ICS/LABA plus Montelukast in Patients with Uncontrolled Severe Persistent Asthma Based on the Serum IL-13 and FEV1. Open Access Maced J Med Sci 2015; 3: 268-72
22. Kharitonov SA, Gonio F, Kelly C, Meah S, Barnes PJ: Reproducibility of exhaled nitric oxide measurements in healthy and asthmatic adults and children. Eur. Respir J 2003; 21: 433-438
23. Syk J, Malinovschi A, Johansson G, Unden AL, Andreasson A, Lekander M, Alving K: Anti-inflammatory treatment of atopic asthma guided by exhaled nitric oxide: a randomized, controlled trial. J Allergy Clin. Immunol. Pract 2013; 1: 639-648

15. SUPPLEMENTS/APPENDICES

Consent Form

Case Report Forms