ASTHMA AND ALLERGIC DISEASES COOPERATIVE RESEARCH CENTER

Therapeutic Control of Aspirin-Exacerbated Respiratory Disease

VERSION 7.0/07/24/2020

IND# 135837

Study Sponsor(s): The National Institute of Allergy and Infectious Diseases (NIAID)
NIAID Funding Mechanism: U19 Grant **NCT#:** 03326063

IND Sponsor/Number: Elliot Israel, MD/IND#135837

Study Drug Manufacturer/Provider: Cumberland Pharmaceuticals

PREFACE

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ASTHMA AND ALLERGIC DISEASES COOPERATIVE RESEARCH CENTER

AADCRC-BWH-02

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INVESTIGATOR SIGNATURE PAGE	
Protocol #:	**Version/Date:** 7.0/07/24/2020
Site Principal Investigator: Elliot Israel, MD	
Title: Therapeutic Control of Aspirin-Exacerbated Respiratory Disease	
Study Sponsor: The National Institute of Allergy and Infectious Diseases (NIAID)	

INSTRUCTIONS: *The site Principal Investigator should print, sign, and date at the indicated location below. A copy should be kept for your records and the original signature page sent. After signature, please return the original of this form by surface mail to:*

DAIT Regulatory Management Center
Pharmaceutical Product Development
3900 Paramount Parkway
Morrisville, NC 27560

I confirm that I have read the above protocol in the latest version. I understand it, and I will work according to the principles of Good Clinical Practice (GCP) as described in the United States Code of Federal Regulations (CFR) – 45 CFR part 46 and 21 CFR parts 50, 56, and 312, and in the International Conference on Harmonization (ICH) document *Guidance for Industry: E6 Good Clinical Practice: Consolidated Guidance* dated April 1996. Further, I will conduct the study in keeping with local legal and regulatory requirements.

As the site Principal Investigator, I agree to carry out the study by the criteria written in the protocol and understand that no changes can be made to this protocol without the written permission of the IRB and NIAID.

_____

Site Principal Investigator (Print)

_____ _____

Site Principal Investigator (Signature) **Date**

Protocol Synopsis

Title	Therapeutic Control of Aspirin-Exacerbated Respiratory Disease
Short Title	Aspirin-Exacerbated Respiratory Disease
Clinical Phase	Phase II
Number of Sites	N=1
IND Sponsor/Number	Elliot Israel, MD/IND#135837
Study Objectives	1. To determine the efficacy of ifetroban as a treatment for patients with AERD. 2. To determine the relevance of TP receptor signaling, and the effect of TP receptor blockade, on platelet and mast cell activation, mediator generation, release of IL-33, and cell recruitment in subjects with AERD, in regard to their chronic respiratory symptoms and during clinical reactions to aspirin.
Study Design	The protocol involves a 4-week, double-blind, placebo-controlled parallel-design trial of oral ifetroban in patients with AERD. At the end of the 4-week treatment phase (ifetroban or placebo) each subject will undergo a graded oral aspirin desensitization procedure in order to initiate high-dose aspirin therapy, which is standard-of-care at our institution and is the only available therapy known to modify the course of AERD.
Primary Endpoint(s)	The calculated dose of aspirin that induces an increase in the Total Nasal Symptom Score (TNSS) of 2 from the pre-aspirin challenge value, "PD_2"
Secondary Endpoint(s)	1. Severity of bronchoconstriction (as measured by maximum fall in FEV_1 during the aspirin-induced reaction) during the aspirin-induced reaction at Visit 2, compared between patients on placebo vs ifetroban, with the changes also analyzed with provocative aspirin dose as a covariate. 2. Increase of urinary, and nasal lavage levels of LTE_4 during aspirin-induced reaction from Visit 2 pre-aspirin levels, compared between patients on placebo vs ifetroban, with the changes also analyzed with provocative aspirin dose as a covariate. 3. Change from Visit 1 in baseline FEV_1, Asthma Control Questionnaire (ACQ), and Sino-Nasal Outcome Test (SNOT-22) at Visit 2, compared between patients on placebo vs ifetroban. 4. Change in levels of other urinary, and nasal eicosanoids, and levels of plasma/serum and nasal tryptase, from Visit 1 to Visit 2 pre-aspirin challenge and Visit 2 pre-aspirin to during the aspirin-induced reaction at Visit 2, compared between patients on placebo vs ifetroban, with the changes also analyzed with provocative aspirin dose as a covariate. 5. Change from Visit 1 in baseline exhaled nitric oxide (FeNO) levels at Visit 2, compared between patients on placebo vs ifetroban.

	6. Change in numbers/percentages of activated platelets and platelet-leukocyte aggregates in the peripheral blood from Visit 1 to Visit 2 baseline (pre-aspirin administration) and during the aspirin-induced reaction at Visit 2 from Visit 2 baseline, compared between patients on placebo vs ifetroban, with the changes also analyzed with provocative aspirin dose as a covariate.
Accrual Objective	50 subjects
Study Duration	36 months
Treatment Description	Ifetroban and aspirin
Inclusion Criteria	1. History of AERD, defined as meeting the diagnostic triad with: 1. History of physician-diagnosed asthma and 2. History of physician-diagnosed nasal polyposis and 3. History of pathognomonic reactions aspirin or other nonselective COX inhibitors. 2. Stable asthma (post-bronchodilator FEV_1 of ≥70%, no glucocorticoid burst for at least 2 weeks prior to Visit 1, and no hospitalizations or ER visits for asthma for at least the prior 6 months) 3. Age between 18 and 70 years 4. No current smoking (not more than one instance of smoking in the last 3 months) 5. Non-pregnant
Exclusion Criteria	1. Hypersensitivity to montelukast 2. Current use of zileuton 3. History of bleeding diathesis or use of anticoagulant or antiplatelet drugs 4. Current use of any NSAIDs aside from the aspirin provided during the study 5. Current use of beta blockers 6. Use of any biologics within the last 4 months prior to initiating the study 7. Heart rate of <50bpm at Screening Visit or evidence of any type of heart block at Screening. 8. Evidence of liver failure (AST or ALT levels >3x normal at Screening) 9. Evidence of kidney failure (creatinine levels >1.5mg/dl in women and >1.7mg/dl in men)
Study Stopping Rules	The study PI or ISM may terminate this study at any time. Reasons for termination may include, but are not limited to the incidence or severity of AEs in this study indicating a potential health hazard to subjects or unsatisfactory subject enrolment. Any serious and/or persistent noncompliance by the investigator with the protocol, the clinical research agreement, the Form FDA 1572, or other local applicable regulatory guidelines in conducting the study may also be grounds for termination of the study. The PI will promptly inform all other investigators conducting the study if the study is suspended or terminated for safety reasons, and will also inform the regulatory authorities of the suspension or termination of the study and the reason(s) for the action.

	Study enrollment, investigational drug, and study procedures will be suspended pending expedited review of all pertinent data by the IRB and the NIAID, if any one of the following occurs: 1. If any death occurs that is designated as related to ifetroban or to a study procedure. 2. If 3 AERD enrolled trial participants experience serious non-fatal AEs related to aspirin desensitization, or if 2 AERD enrolled participants experience serious non-fatal AEs related to ifetroban/placebo, or to another study procedure.

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Table of Contents

Glossary of Abbreviations

CFR	Code of Federal Regulations
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DAIT	Division of Allergy, Immunology, and Transplantation
DSMB	Data Safety Monitoring Board
FDA	Food and Drug Administration
GCP	Good Clinical Practice
ICH	International Conference on Harmonization
IND	Investigational New Drug
IRB	Institutional Review Board
MOP	Manual of Procedures
NIAID	National Institute of Allergy and Infectious Diseases
PI	[Site] Principal Investigator
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Suspected Adverse Reaction
SOP	Standard Operating Procedure
SUSAR	Serious Unexpected Suspected Adverse Reaction

Study Definitions Page *[Optional]*

Lost to Follow-up	
Medical Monitor	
NIAID Project Manager	
Principal Investigator	
Program Officer	
Protocol Mandated Procedures	
Randomized	
Regulatory Affairs Officer	
Site Principal Investigator	
Site Study Coordinator	
Study Termination	
Study Therapy	
Withdrawal from Therapy	

1. Background and Rationale

1.1. Background and Scientific Rationale

Aspirin-exacerbated respiratory disease (AERD) is highly overrepresented in populations with severe asthma, refractory sinusitis, and nasal polyposis.[1,2] There are few available therapeutic options. AERD is typified by sinonasal dysfunction, asthma, eosinophilic respiratory tract inflammation, overproduction of cysteinyl leukotrienes (cysLTs), as determined by high levels of urinary leukotriene (LT)E_4, and persistent release of mast cell products (histamine, tryptase, and prostaglandin (PG)D_2) in the absence of exposure to aspirin. The reactions to aspirin and other nonselective cyclooxygenase (COX) inhibitors are associated with bronchoconstriction and worsening congestion, rhinorrhea, sneezing, and ocular symptoms. These reactions are accompanied by further explosive tissue mast cell activation and cysLT generation. Although CysLT_1R antagonists are widely used in AERD, they rarely improve basal symptoms, provide only partial protection from aspirin-induced bronchoconstriction,[3] and do not prevent sinonasal and ocular features of reactions to aspirin.

CysLT overproduction is a hallmark of AERD, and cysLTs are important mediators of the pathognomonic reactions to COX-1 inhibitors, as well as of some features of the chronic disease state. Overexpression of LTC_4S by eosinophils,[4] increased conversion of granulocyte-derived LTA_4 to LTC_4 by adherent LTC_4S-expressing platelets,[5] and failure to maintain tissue levels of COX-2-derived PGE_2 sufficient to suppress 5-lipoxygenase (LO) activity and mast cell activation[6,7] all likely contribute to dysregulated cysLT synthesis in AERD. As a result, further depletion of PGE_2 by aspirin or other COX-1-active drugs results in a stereotypical respiratory reaction accompanied by dramatic increases in urinary LTE_4 [8] However, while the 5-LO inhibitor zileuton and CysLT_1R antagonists can attenuate physiologic responses to aspirin challenge in AERD, they are neither uniformly effective nor disease-modifying, and they frequently fail to control the severe sinus disease and asthma that are typical chronic features.[3,9,10] Moreover, high-dose aspirin treatment after desensitization, the only modality that prevents recurrence of nasal polyps in AERD,[11] does not suppress basal cysLT production,[12,13] although it does reduce pulmonary reactivity to LTE_4 [14] and nasal mucosal expression of CysLT_1R.[15] Additionally, 30% of subjects do not benefit from high-dose aspirin treatment.[11] Additional insights into disease mechanism(s) are urgently needed in order to develop new therapies.

Although AERD pathogenesis clearly involves mediators other than cysLTs and cysLT receptors other than CysLT_1R, the limited availability of selective antagonists has precluded analyses of these mediators and receptors in humans. Both our preliminary studies and our recent publications[12,16] implicate two T prostanoid (TP) receptor ligands, PGD_2 and thromboxane (TX)A_2, as central mediators and important potential therapeutic targets in AERD. TP receptors and cysLTs act as components of a hierarchical, feed-forward network of mediators and cells that drive the persistent respiratory inflammation, tissue remodeling, end-organ dysfunction, and clinical reactions to COX-1 inhibitors that define AERD. TP receptor ligands may also be responsible for some features of aspirin reactions that resist blockade of CysLT_1R. We will validate our predictions in a carefully phenotyped cohort of subjects with AERD and will test the efficacy of a safe, novel potential treatment that is based on strong biological plausibility. Completion of these studies will substantially advance our knowledge of the mechanisms that drive the persistent baseline features of the disease (respiratory tract inflammation, disturbed lipid mediator metabolism) and the clinical reactions to aspirin (mast cell and platelet activation, incremental release of eicosanoids and IL-33). Additionally, since the implicated mechanisms apply to innate type 2 immunity and overlap substantially with severe asthma in general, the knowledge gained will have immeasurable added value.

1.2. Rationale for Selection of Investigational Product or Intervention

TP receptors are G protein-coupled receptors (GPCRs) that are expressed by platelets, endothelial cells, cholinergic nerves,[17] naive T cells,[18] and both bronchial and vascular smooth muscle cells. They bind TXA_2 with high affinity, and also bind isoprostanes (PG-like arachidonic acid-derived products generated nonenzymatically by oxidative stress).[19] Two TP receptor isoforms (TPα and TPβ) arise from alternative splicing of a single gene, producing receptors with different C-terminal sequences.[20] TP signaling induces/amplifies platelet aggregation in response to multiple stimuli, and upregulates adhesion receptor expression by lung vascular endothelial cells.[21] TP signaling also constricts human and rodent bronchi by both neurally-mediated pathways[17,22] and by direct smooth muscle stimulation.[23] Interestingly, multiple PGs (PGD_2, PGF_2, high-dose PGE_2) require TP receptors to contract human bronchi ex vivo.[24] Thus, TP receptor antagonism may broadly alter physiologic responses in contexts where contractile prostaglandins are generated at high levels, such as AERD **(Figure 1)**.[12]

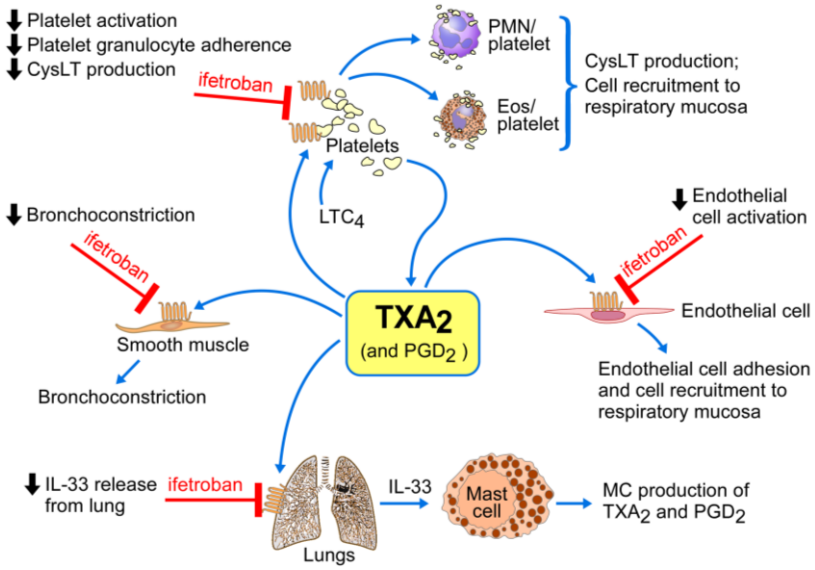

Figure 1. Overview of role of TP receptors and their ligands in AERD pathogenesis.

This proposal directly tests the central hypothesis using new tools and approaches we have developed during the current period of support. Combining mechanistic information from our mouse model with studies carried out on a cohort of subjects with AERD, we have identified several readouts that likely reflect, at least in part, the signatures of TP receptor actions in AERD in vivo. These include changes in the numbers of circulating effector cell populations during clinical reactions (a real-time measure of cell recruitment), changes in the levels of eicosanoid receptor expression by these cells (reflecting in vivo exposure to their ligands released during reactions), and intravascular platelet activation (potentially requiring TP signaling for amplification). With the aid of **Core C**, we will monitor urinary and nasal lavage levels of TP-active eicosanoids (PGD_2, TXA_2), as well as cysLTs, which will enable us to determine whether cysLTs act upstream or downstream of TP ligands. By combining a pivotal proof-of-concept trial with real-time monitoring of these surrogates, along with established physiological (changes in lung function, nasal symptoms) and biochemical (mast cell activation products) readouts, this project gains essential new knowledge of AERD pathophysiology. It also addresses a substantial unmet need by introducing a safe and potentially efficacious new treatment for AERD that is based on principles supported by our own studies. The mechanistic studies proposed will verify whether TP blockade (as we suspect) will interrupt the feed-forward system that drives persistent activation of the innate immune system, mast cell mediator release, platelet activation, and cysLT overproduction that characterize AERD **(Figure 1)**.

1.3. Preclinical Experience

Our preclinical studies in the previous AADCRC strongly suggest that TP receptors play an essential role in AERD. Mouse studies demonstrate that TP signaling acts *upstream* of cysLTs to initiate LTC_4 formation during reactions to aspirin (likely through effects on platelet-adherent leukocytes), as well as *downstream* of the cysLTs (via $CysLT_2R$), permitting effector functions of TP-active PGs at endothelial cells, smooth muscle, and perhaps other targets.[25,26]The latter effects include induction of lung IL-33 expression, which amplifies eosinophilia and drives mast cell activation with aspirin challenges.[27] In the mouse model, endogenous cysLTs signal through $CysLT_2R$ to drive TXA_2 generation by platelets.[26,28] TXA_2 may then amplify IL-33 generation through TP receptors. This putative TP-mediated feed-forward loop may explain why long-term

blockade of TP receptors (or their deletion) suppresses pulmonary eosinophilia and prevents aspirin sensitivity in *Ptges*$^{-/-}$ mice.[25] We have found that ifetroban, the agent used in this proposal, blocks all features of reactions to aspirin in AERD-like *Ptges*$^{-/-}$ mice when administered in drinking water overnight, including cysLT and PGD_2 generation, release of mast cell and platelet products, and (most importantly), change in airway resistance **(Figure 2)**. We had obtained similar results with SQ29,548, another TP antagonist, in our previous study.[16] These exciting preclinical findings compel us to determine the role of TP and the efficacy of TP blockade in AERD in this Project.

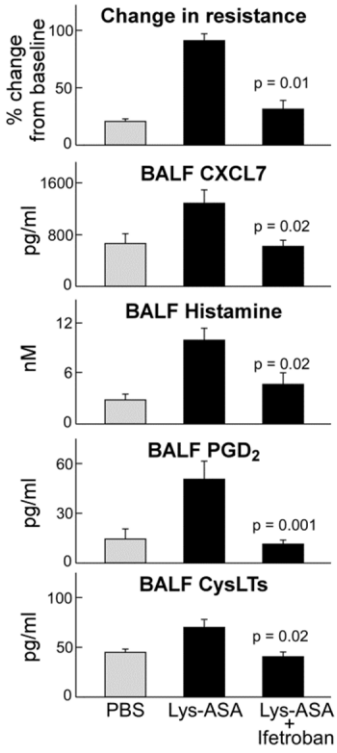

Figure 2. Blockade TP receptors abrogates aspirin sensitivity in PGE_2-deficient mice. Peak change in lung resistance (R_L) (top) in response to challenges of *Ptges*$^{-/-}$ mice with aerosolized Lys-ASA or PBS 24h after the last of 6 treatments with *Df*. Some mice received ifetroban in drinking water (25 mg/ml) for 2 d before challenge. Levels of the indicated mediators were measured in the BAL fluid (BALF) from the same mice. Results are from 5 mice per group.

1.4. Clinical Studies

Ifetroban is a potent, selective TP receptor antagonist. It was the subject of extensive preclinical and clinical development for cardiovascular patients in the 1990s and a large safety database exists from this work, but development for cardiovascular applications was discontinued due to business reasons. In 2009, Cumberland Pharmaceuticals Inc. acquired ownership of the ifetroban program. A phase 2 trial to determine the safety of oral ifetroban in 16 subjects with AERD (NCT02216357) completed in December 2015 and showed no adverse effects.

Ifetroban is rapidly and almost completely (91%) absorbed after oral administration of a 50 mg dose, and the absolute bioavailability of the capsule formulations is 42%. The half-life of ifetroban is similar after IV and oral administration (22 hours). The volume of distribution, 4.4 L/kg, is much larger than total body water indicating that the drug distributes into tissues. Ifetroban is eliminated primarily by metabolism and biliary excretion with 30% of the dose excreted in the urine (< 4% as unchanged drug) and the remainder excreted in the feces.

See Section *Risks of Investigational Product or Intervention as cited in Investigator Brochure or Package Insert for further detailed* Clinical Studies.

2. Study Hypotheses/Objectives

2.1. Hypotheses

We will test the central hypothesis that TP receptor signaling on platelets, endothelial cells, and airway smooth muscle promotes persistent eosinophilic respiratory inflammation, drives cysLT overproduction, facilitates release of innate type 2 cytokines downstream of cysLTs and platelets, and mediates bronchoconstriction in response to TXA_2 and PGD_2 released by mast cells during reactions to aspirin in AERD. As such, we expect that TP receptor blockade will interfere with both the cysLT-dependent and -independent features of AERD pathophysiology and will interrupt a feed-forward loop that drives the disease.

2.2. Primary Objective(s)

The primary clinical objective is to determine whether blocking TP receptors with ifetroban attenuates the severity of aspirin-induced respiratory reactions. We will also determine the effect of ifetroban on baseline lung function and symptom control in AERD, as well as changes in urinary and respiratory eicosanoids.

2.3. Secondary Objective(s)

The secondary objective is to determine the relevance of TP receptor signaling, and the effect of TP receptor blockade, on platelet and mast cell activation, mediator generation, release of IL-33, and cell recruitment in subjects with AERD at baseline and during clinical reactions to aspirin.

3. Study Design

3.1. Description of Study Design

The central hypothesis will be tested using a randomized, double-blinded, placebo-controlled trial of ifetroban, a potent, selective TP receptor antagonist,[29,30] in subjects with AERD. We will monitor clinical symptoms and markers of respiratory inflammation to determine the extent to which TP receptor signaling contributes to the chronic pathobiology of the disease. We will also determine whether TP receptor blockade prevents the airflow obstruction and the surge in cysLT generation that accompany clinical reactions to aspirin, as predicted from the murine AERD model. We will monitor platelet and mast cell activation signatures in vivo and will monitor IL-33 release. We serve a large referral population (10-12 new referrals per month to our BWH AERD Center), have all of the tools to test our central hypothesis, and have extensive experience running clinical trials. This project introduces a new potential therapeutic strategy for patients with AERD, therefore addressing an unmet need.

The Study Population will consist of individuals with AERD referred to the BWH Asthma Center, BWH Allergy or Otolaryngology clinics, or the BWH AERD Center for evaluation and potential aspirin desensitization. 50 individuals with

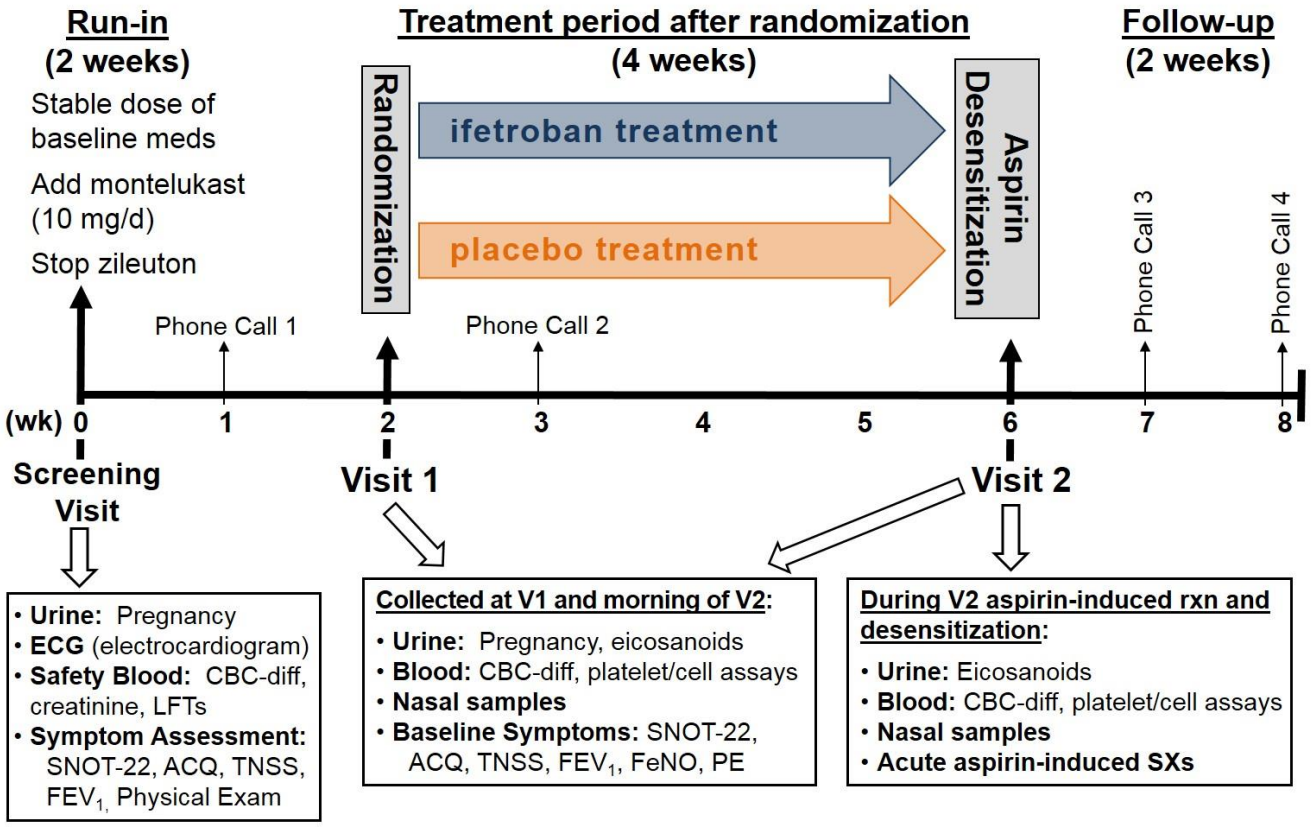

Figure 3. Schematic of Intervention Study. After Run-in, subjects (n=50) will be randomized at Visit 1 to receive ifetroban or placebo for 4 wks. All subjects will be desensitized to aspirin at Visit 2, with detailed evaluations of the

suspected AERD will be enrolled in this study with the anticipation that there will be a dropout rate of 10-20%. All subjects will have a clinical history consistent with AERD (asthma, nasal polyposis, and a history of a suspected reaction to a nonselective COX inhibitor). All subjects will be on standard therapy for persistent asthma, which may include some combination of inhaled glucocorticoids, oral glucocorticoids, long- and short-acting β-agonists, and $CysLT_1R$ antagonists. We will exclude individuals being treated with omalizumab (monoclonal anti-IgE) or mepolizumab (monoclonal anti-IL-5), as the effects of these medications on the aspirin-induced reactions in AERD are not known. Detailed Inclusion and Exclusion criteria are listed in Section 4.2 and 4.3. We have found that all of the subjects who are currently enrolled in our trial of prasugrel and meet these strict inclusion criteria exhibited respiratory reactions to aspirin, confirming their diagnosis of AERD. The Study Schema overview is shown in **Figure 3.**

At a Screening Visit for patients with AERD, the study will be explained, and the participant will sign informed consent before undergoing any procedures. A physical exam, baseline ECG, spirometry and lab work (CBC, urine pregnancy) will be performed. Assessments of asthma control (ACQ score, which evaluates asthma control over the preceding 1 week), and nasal symptoms (SNOT-22 score, which assesses symptoms over the preceding 2 weeks) will also be obtained.

There will be a 2-week Run-In after the Screening Visit during which subjects will begin taking montelukast 10mg daily (if not already on montelukast as part of their regular asthma care) and will stop taking zileuton (if they are on

zileuton as part of their regular asthma care). A telephone encounter **(Phone Call 1)** 1 week later will ensure safety and confirm stable asthma.

After the 2-week Run-In Period on montelukast, subjects will come into the ARC for **Visit 1**. Interval history, physical exam, ACQ, SNOT-22, pre-challenge TNSS and spirometry will be recorded, along with FeNO. Blood will be drawn for CBC/differential, and cellular profiling and activation assays. A urine sample will be collected for pregnancy and eicosanoid metabolites. Nasal lavage for cytokine and eicosanoid measurements and a nasal epithelial scraping sample for RNA extraction will be taken. Subjects will be randomized to receive ifetroban (200 mg dose per day), or placebo for 4 weeks.

Subjects will take ifetroban or placebo daily for 4 weeks and will continue taking daily montelukast. There will be a telephone encounter **(Phone Call 2)** 1 week into this Treatment Period to ensure safety and confirm that chronic asthma symptoms have not worsened.

After the 4-week treatment period, subjects will come into the ARC for **Visit 2.** Before aspirin is given, interval history, physical exam, ACQ, SNOT-22, TNSS, and spirometry will be recorded, along with FeNO, and a urine sample will be collected for pregnancy and eicosanoid metabolites. Nasal lavage and a nasal epithelial scraping sample will also be taken (prior to the TNSS questionnaire to ensure that the procedures do not affect the symptom assessment), along with a blood draw for CBC/differential and cellular assays. After waiting at least 15 minutes following the nasal lavage and scraping so that any nasal irritation has subsided, subjects will then undergo an oral aspirin desensitization procedure. They will receive an initial 40.5 mg dose of aspirin, and then every 90 minutes will be given increasing doses of 81, 162, and 325 mg aspirin. Vital signs are obtained every 90 minutes during the aspirin challenge/desensitization. If at any point the subject develops symptoms of a reaction, we will examine them and record the time of onset of reaction. The dose of reaction that induces an increase in TNSS of 2 or more points will be recorded as the provocative dose.

Following the onset of reaction, patients will be observed for a 3-hour period, during which time no more aspirin doses will be given. TNSS will be recorded at the onset of reaction and again every 30 minutes during this 3-hour period after reaction. Pulmonary function testing is repeated before each dose and at the onset of reaction and if it remains within 85% of their pre-challenge FEV_1, it will be repeated every 90 minutes during the 3-hour period after reaction. If the FEV_1 falls by 15% or more from their morning FEV_1, they will be treated with albuterol, administered by metered dose inhaler (MDI), (up to 8 puffs per administration), and FEV_1 will be repeated every 30 minutes until it has returned to within 85% of their morning pre-challenge FEV_1. If after 3 rounds of albuterol administered by MDI (a total of 24 puffs), the subject's FEV1 has not returned to within 85% of their morning pre-challenge FEV1, nebulized albuterol will be administered. No medications (except albuterol and ipratropium) will be used for relief of symptoms during the desensitization until the 3-hour period of observation following onset of reaction is completed, unless required for a patient's safety. A blood sample will be collected 1 hour after the onset of reaction for CBC/differential, platelet activation assays, and platelet-leukocyte aggregate measurements. Urine and nasal samples will be collected at the onset of reaction, and again 90 minutes and 3 hours after the onset of reaction, or if there is no clinical reaction at all, will be collected 90 minutes after the 325mg dose of aspirin is given.

Upon completion of the 3-hour period of observation, further aspirin doses will be administered every 90 minutes until a state of clinical desensitization to and tolerance of 325 mg of aspirin is achieved. Patients will be discharged home 90 minutes after ingestion of 325 mg of aspirin and will be instructed to begin taking daily aspirin, as is part of our standard-of-care for these patients. If required due to time constraints, this visit could proceed onto the next day, during which the subject would begin by repeating the aspirin dose they ended with the day before. However, 95% of our aspirin desensitization procedures done as part of clinical patient care are completed within the first day.

We anticipate it will take us 36 months to recruit 45-50 subjects with AERD into this study to complete the 4-week treatment phase and the aspirin desensitization, with a plan to enroll 1-2 subjects/month (15/year). Based on the monthly patient referral volume at our BWH AERD Center and our success in recruiting for our current study, our recruitment goal is readily achievable (**Table 1**).

Table 1: Timeline for AERD study

Pre-Award		Submit IND	
Year 1	Q1	Submit protocol and Consent Form to DSMB	Development of IRB documents; CRF and database development
	Q2		
	Q3	Submit DSMB-approved Consent and protocol to IRB	
	Q4		Hiring/training as needed
Year 2, 3, 4		Recruitment (last patient completes in Q4 of Year 4)	
Year 5	Q1	Data analysis and clean-up	
	Q2		
	Q3	Writing of final study reports	
	Q4		

3.2. Primary Outcome

The primary outcome is the calculated dose of aspirin that induces an increase in the Total Nasal Symptom Score (TNSS) of 2 from the baseline value, or "PD_2".

The PD_2 will be calculated during the aspirin desensitization at Visit 2 as follows:

$$inverselog_{10}\left(\frac{\left(2-(PrevTNSS-BaselineTNSS)\right)\times(log_{10}ProvocDose-log_{10}PrevDose)}{(MaxTNSS-BaselineTNSS)-(PrevTNSS-BaselineTNSS)}+(log_{10}PrevDose)\right)$$

Where:

Baseline TNSS = TNSS score prior to administration of aspirin

PrevTNSS = TNSS score immediately previous to onset of aspirin reaction

MaxTNSS = Maximum TNSS score recorded during 3-hour observation period during aspirin reaction

ProvocDose = Dose of aspirin that provoked a reaction

PrevDose = Dose of aspirin that preceded the provocative dose

We have used this outcome in our current nearly completed study of 40 patients with AERD and have found that it is an accurate reflection of reaction severity and aspirin sensitivity. As PD_2 is based both on the provocative dose of aspirin that induced a reaction and on the severity of the reaction, it reflects each patient's sensitivity to aspirin. Nasal and upper respiratory symptoms (congestion, rhinorrhea, sneezing, nasal and ocular itching) in response to the provocative dose of aspirin will be monitored based on a 0- to 5-point scale (0, none; 1, little; 2, moderate; 3, quite a bit; 4, severe; 5, very severe) as described.[31] The maximum TNSS possible (indicating maximal symptoms) is 40.

3.3. Secondary Outcomes

The secondary outcomes include the following:

- The severity of bronchoconstriction (measured by maximum percent fall in FEV_1) during the aspirin-induced reaction at Visit 2, compared between patients on placebo vs ifetroban.
- Increase in urinary and nasal levels of cysLTs during aspirin-induced reaction at Visit 2 from Visit 2 pre-aspirin levels, compared between patients on placebo vs ifetroban, as a proof-of-mechanism that TP receptor signaling in AERD drives cysLT overproduction.
- Change in levels of other urinary and nasal eicosanoids, and levels of plasma/serum and nasal tryptase, both from Visit 1 to Visit 2 prior to aspirin administration and also from Visit 2 prior to aspirin administration to during aspirin-induced reactions at Visit 2, compared between patients on placebo vs ifetroban.
- Change in numbers/percentages of activated platelets and platelet-leukocyte aggregates in the peripheral blood between Visit1 and Visit 2 baseline (pre-aspirin administration) and Visit 2 baseline and during the aspirin-induced reaction at Visit 2, compared between patients on placebo vs ifetroban.

- Change in baseline (pre-aspirin administration) FEV_1, Asthma Control Questionnaire (ACQ), and Sino-Nasal Outcome Test (SNOT-22) at Visit 2 from Visit 1, compared between patients on placebo vs ifetroban.
- Change in Visit 2 baseline (pre-aspirin administration) levels of exhaled nitric oxide (FeNO) from Visit 1, compared between patients on placebo vs ifetroban.
- For each secondary endpoint above, which compares the aspirin-induced changes during the aspirin-induced reaction at Visit 2 for patients on placebo vs ifetroban, we will also analyze these changes with provocative aspirin dose as a covariate. We will treat provocative aspirin dose as level variable: in log scale, if the aspirin doses are 40.5, 81, 162, and 325, we will code the dose variable as dose 1, 2, 3 and 4 assume each increase in dose is linear.

3.4. Exploratory Outcomes

The exploratory outcomes include the following:

- Plasma and nasal lavage levels of IL-33 , and platelet products, as measured at baseline (pre-aspirin administration) and during aspirin-induced reactions at Visit 2, compared between patients on placebo vs ifetroban.
- Other inflammatory mediator levels in plasma, nasal lavage, and urine, as measured at baseline (pre-aspirin administration) and during aspirin-induced reactions at Visit 2, compared between patients on placebo vs ifetroban.
- Levels of surface expression of eicosanoid *r*eceptors by effector cells (eosinophils, basophils, and ILC2s) in the peripheral blood at baseline (pre-aspirin administration) and during the aspirin-induced reaction at Visit 2, compared between patients on placebo vs ifetroban.
- For each exploratory endpoint above, which compares the aspirin-induced changes during the aspirin-induced reaction at Visit 2 for patients on placebo vs ifetroban, we will also analyze these changes with provocative aspirin dose as a covariate. We will treat provocative aspirin dose as level variable: in log scale, if the aspirin doses are 40.5, 81, 162, and 325, we will code the dose variable as dose 1, 2, 3 and 4 assume each increase in dose is linear.

3.5. Stratification, Randomization, and Blinding/Masking

We will use block randomization in groups of four, ensuring that equal numbers of subjects are randomized to each group. For this two-arm balanced-design study, the randomization will consist of blocks of 4 patients randomly assigned (allocation ratio of 1:1) to ifetroban or placebo. Matching capsules of ifetroban and placebo will be supplied by Cumberland Pharmaceuticals and provided to the BWH Investigational Drugs Services pharmacy (IDS) for storage and distribution. The IDS will conduct the randomization and keep records to maintain study blinding.

3.5.1. Procedure for Unblinding/Unmasking

Unblinding must be approved by the study Medical Monitor unless an immediate life threatening condition has developed and the Medical Monitor is not accessible. In case of an emergency where a subject needs to be unblinded, the PI or physician co-investigators may contact IDS to unblind the subject. The IDS pharmacist is on call 24 hours a day. The PI will notify the protocol chair of the unblinding event on the next business day.

A full account of the event will be recorded, including the date and time of the unblinding, the reason for the decision to unblind, and the name of the individual who made the decision and the names of the Medical Monitor and others who were notified. The reasons for unblinding of a participant's treatment will be included in the final study report.

Unblinding of the entire study will require written approval from NIAID.

4. Selection of Participants and Clinical Sites/Laboratories

4.1. Rationale for Study Population

Since AERD is virtually always an adult-onset disease, adults will comprise all of the study subjects. AERD affects both sexes and all races; no exclusions will be made based on sex or ethnicity.

4.2. Inclusion Criteria

Individuals who meet all of the following criteria are eligible for enrollment as study participants:

1. Subject must be able to understand and provide informed consent
2. Age between 18 and 70 years
3. History of AERD, defined as meeting the diagnostic triad with:
    a. History of physician-diagnosed asthma **and**
    b. History of physician-diagnosed nasal polyposis **and**
    c. History of pathognomonic reactions to aspirin or other nonselective COX inhibitors.

    To ensure all patients stringently meet this criteria and truly have AERD, we will require that patients either:

    1. Have a history of at least two pathognomonic clinical reactions to aspirin or other nonselective COX inhibitors with features of lower (cough, chest tightness, wheezing, dyspnea) and/or upper (rhinorrhea, sneezing, nasal obstruction, conjunctival itching and discharge) airway involvement. Or...
    2. Have had a confirmatory physician-administered challenge with aspirin or another nonselective COX inhibitor that induced a pathognomonic respiratory reaction as above.
4. Stable asthma (post-bronchodilator FEV_1 of ≥70%, no glucocorticoid burst (increase ≥ 10mg per day or doubling daily dose, whichever is less) for at least 2 weeks prior to Visit 1, and no hospitalizations or ER visits for asthma for at least 6 months prior to Visit 1), and for those patients on daily oral steroids, they must require no more than a daily dose of 10mg prednisone or equivalent for their standard daily therapy to be considered for inclusion.
5. For females: Non-pregnant and practicing adequate birth control or abstinence
6. For males: practicing adequate birth control or abstinence
7. No current smoking (not more than one instance of smoking in the last 3 months)

4.3. Exclusion Criteria

Individuals who meet any of these criteria are not eligible for enrollment as study participants:

1. Inability or unwillingness of a participant to give written informed consent or comply with study protocol
2. Hypersensitivity to montelukast
3. Current use of zileuton (which blunts the peak levels of urinary LTE_4 during reactions)
4. Any history of bleeding diathesis or current use of anticoagulant/antiplatelet drugs
5. Any history of gastrointestinal bleeding
6. Current use of oral beta blockers, though opthalmic formulations are acceptable

7. The use of an additional non-steroidal anti-inflammatory drugs (NSAIDs), except the aspirin dosing as detailed for the study
8. Use of any biologic therapy within the prior 4 months (120 days) of Visit 1.
9. History of cardiac rhythm disturbances.
10. Heart rate of <50 bpm at Screening Visit, or evidence of any type of heart block on ECG at Screening Visit.
11. Pregnant, nursing, or planning to become pregnant.
12. Past or current medical problems or findings from physical examination or laboratory testing that are not listed above, which, in the opinion of the investigator, may pose additional risks from participation in the study, may interfere with the participant's ability to comply with study requirements or that may impact the quality or interpretation of the data obtained from the study.
13. Evidence of liver failure (AST or ALT levels >3x normal at Screening)
14. Evidence of kidney failure (creatinine levels >1.5mg/dl in women and >1.7mg/dl in men)

5. Known and Potential Risks and Benefits to Participants

5.1. Risks of Investigational Product or Intervention as cited in Investigator Brochure or Package Insert

Risks of Ifetroban:

The pharmacodynamics of ifetroban were studied in single- and repeat-dose safety studies and in an ifetroban and aspirin interaction study in healthy volunteers. In the single-dose study, bleeding time was prolonged (2x baseline) in subjects receiving doses of ifetroban greater than 10 mg. Platelet aggregation induced by the TP receptor agonist U46619 was inhibited by all doses of ifetroban including 10 mg. This effect lasted for up to six days for the highest dose (1000 mg). Ifetroban also blocked arachidonic acid-induced platelet aggregation and partially inhibited collagen-induced aggregation. While epinephrine-induced primary aggregation was not affected by ifetroban, the secondary aggregation (degranulation) appeared to be inhibited. There was no drug effect on ADP-induced aggregation. Ifetroban alone or in combination with aspirin inhibited U46619-induced platelet aggregation. Treatment with aspirin alone did not prevent U46619-induced aggregation. Bleeding time was prolonged after all doses following the single dose and at steady state, although no dose-dependent increase in bleeding time was observed. No indication of accumulation effect was seen after nine days of dosing. No significant effect on urinary excretion of TXA_2 and prostacyclin metabolites was observed. In the aspirin interaction study, urinary excretion of both 2,3-dinor-TXB_2 and 2,3-dinor-6-keto-$PGF_{1\alpha}$ was decreased after administration of 325 mg of aspirin alone and 325 mg of aspirin + 250 mg ifetroban. Administration of ifetroban alone had no effect on urinary excretion of either 2,3-dinor-TXB_2 or 2,3-dinor-6-keto-$PGF_{1\alpha}$. Thus, TP receptor blockade has no effect on the synthesis of vasoprotective PGI_2. *Of specific importance to our proposed trial, no significant safety concerns emerged in the studies of ifetroban with aspirin*.

Ifetroban was the subject of 24 controlled and uncontrolled human pharmacology and pharmacokinetic studies. It was also the subject of eight placebo-controlled clinical trials for various cardiovascular indications which are summarized in **Table 2**. The incidence rate of adverse events was generally comparable between the ifetroban-treated subjects and the placebo-treated subjects. Bradycardia was reported more often in the ifetroban group (N=32; 3.3%) than with placebo (N=7; 1.2%). Gastrointestinal events tended to occur more often in the ifetroban subjects than in the placebo subjects, although incidence rates were too small to suggest a trend or pattern. The most frequently reported adverse events (N; % ifetroban vs. N; % placebo) were headache (N=80; 8.4 vs. N=47; 7.7), musculoskeletal pain (N=48; 5.0 vs. N=19; 3.1), angina pectoris (N=33; 3.5 vs. N=22; 3.6), bradycardia (N=32; 3.3 vs. N=7; 1.2), myocardial infarction (N=28; 2.9 vs. N=18; 3.0), nausea/vomiting (N=25; 2.6 vs. N=10; 1.6), dyspepsia (N=24; 2.5 vs. N=9; 1.5), upper respiratory infection (N=24; 2.5 vs. N=9; 1.5), hematoma (N=23; 2.4 vs. N=8; 1.3), coronary artery bypass (N=22; 2.3 vs. N=10; 1.6), coronary angioplasty (N=21; 2.2 vs. N=10; 1.6), abdominal pain (N=20; 2.1 vs. N=10; 1.6), and anxiety/nervousness (N=19; 2.0 vs. N=9; 1.5). All remaining events occurred at a rate less than 2.0% in both treatment groups except for dizziness which occurred in 2.1% (N=13) of placebo-treated subjects (ifetroban: N=13; 1.9%).

Table 2. Number of subjects exposed to ifetroban in clinical studies.	Subject Exposure	
	Ifetroban	Placebo
Clinical Pharmacology/Pharmacokinetics		
Human Pharmacology	189	49
Pharmacokinetic	154	0
Clinical Trials		
Silent Ischemia (CV124-008)	58	55
Stable angina (CV124-009)	105	52
Unstable angina (CV124-011)	315	166
PTCA (CV124-012)	90	35
PVD (CV124-014)	137	44
Post MI (CV124-015)	149	149
Forearm blood flow in HF (CV124-018)	20	23
Venous ulcers (CV139-001)	82	83
Total Subjects	**1299**	**656**

5.1.1. Reproductive Risks and Toxicology for Ifetroban

Reproductive Risks:

Pregnant and nursing females will not be included in clinical trials of ifetroban. Furthermore, sexually active enrollees should be counselled against either becoming pregnant or fathering a child while participating in ifetroban clinical trials. Acceptable methods of male birth control include abstinence, 3-months post vasectomy, or condom use in combination with spermicide. Females of nonchildbearing potential may be allowed to participate provided that they are either 12-months post-menopausal prior to the first dose of study drug or have been surgically sterilized (e.g. tubal ligation or hysterectomy). Females of childbearing potential may be allowed to participate provided they use an acceptable method of contraception. Acceptable female methods of birth control include abstinence, condom used in combination with spermicide, oral contraceptives or contraceptive patch, contraceptive ring, or an implanted intrauterine device. Ifetroban appears to be teratogenic in rodents. Embryo-fetal toxicity was observed at doses of 100 and 1000 mg/kg administered orally by gavage once daily during gestation and maternotoxicity was seen at the 1000 mg/kg dose. No drug-related changes in the dams or fetuses were seen at the 10 mg/kg level. While these levels are well in excess of those studied in clinical trials thus far, the effects of ifetroban on human fetal development are unknown.

Rat Model

An initial teratology study in rats examined once daily doses (750 and 1500 mg/kg) of ifetroban administered by oral gavage to presumed pregnant rats on days 6 through 15 of gestation. There was a high incidence of resorptions at the doses studied (Lochry 1993, Internal Report 93012).

A reproductive toxicity study conducted in rats investigated once daily doses of ifetroban administered by oral gavage (7, 70, and 700 mg/kg) to both male and female rats prior to mating (4 week in males and 2 week in females) and during gestation. No reproductive effects in terms of fertility or early embryonic development were detected (Lochry 1995, Internal Report 94020).

In a second reproductive toxicity study, rats were given once daily doses (7.5, 75, 750 mg/kg) of ifetroban by oral gavage (gestation days 6-21) were well tolerated at doses up to 75 mg/kg. At 750 mg/kg, ifetroban was deemed toxic resulting in mortality, body weight loss, and enlarged adrenals and kidneys in the dams and an increased frequency of stillbirths and poor pup survival in the offspring (Gietl 1996, Internal Report 95201).

In a study of embryo-fetal development in rats, ifetroban was administered orally by gavage to presumed-pregnant rats once daily on days 6 through 15 of gestation at doses of 10, 100, or 1000 mg/kg. There were no drug-related changes in the dams or fetuses at 10 mg/kg. At 100 mg/kg, maternal liver weights were increased and the offspring demonstrated dilated lateral ventricles in the brain. At 1000 mg/kg, the dams again demonstrated increased liver weights as well as mortality associated with stomach lesions (concretions, ulcers, perforations, thickened mucosa, and/or multifocal discoloration of the stomach); body-weight loss; decreased food consumption; increased incidences of chromodacryorrhea, piloerection, and salivation or regurgitation of the dosing solutions; and increased kidney and spleen weights. Embryo-fetal toxicity at 1000 mg/kg included increased resorptions with an associated decrease in live-litter size, enlarged subarachnoid space of the brain, irregular ossification of the sternum, and decreased fetal weights with related developmental delays in ossification of the vertebrae, sternebrae, metacarpals, metatarsals, and phalanges. Ifetroban is therefore considered teratogenic in rats (Internal Report 94211, Feb 1996).

Rabbit Model

A reproductive toxicity study conducted in rabbits investigated once daily doses of ifetroban administered by oral gavage (4, 40, and 400 mg/kg) to presumed pregnant females on days 6 through 18 of gestation. No changes were seen in animals receiving either 4 or 40 mg/kg. At 400 mg/kg, maternal findings included body weight loss and decreased food consumption and the offspring demonstrated sternal defects (Jahn 1995, Internal Report 94207).

5.2. Risks of Investigational Product or Intervention cited in Medical Literature

5.3. Risks of Other Protocol Specified Medications

Risks of montelukast. Montelukast is a widely prescribed, once daily oral therapy approved for the treatment of asthma and allergic rhinitis. It is commonly prescribed as a treatment for AERD because of the established prominent role for the cysLTs in the disease. It is useful for reducing the severity of bronchoconstrictor responses to aspirin administration, likely due to its ability to competitively antagonize the effects of LTC_4 and LTD_4 acting at $CysLT_1R$. Montelukast is generally safe and well tolerated. The most common adverse reactions to montelukast identified in placebo-controlled trials (incidence ≥ 5% and greater than placebo**;** listed in descending order of frequency) were upper respiratory infection, fever, headache, pharyngitis, cough, abdominal pain, diarrhea, otitis media, influenza, rhinorrhea, sinusitis,

and otitis. Additional reactions reported voluntarily during post-approval use of montelukast are of unknown frequency, and causality is not established. These include increased bleeding tendency, hypersensitivity reactions including anaphylaxis, hepatic eosinophilic infiltration, agitation including aggressive behavior or hostility, anxiousness, depression, dream abnormalities, hallucinations, insomnia, irritability, restlessness, somnambulism, suicidal thinking and behavior (including suicide), tremor, drowsiness, paresthesia/hypoesthesia, seizures, palpitations, epistaxis, diarrhea, dyspepsia, nausea, pancreatitis, vomiting, and hepatitis. Cases of eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome) have been reported as well. Most, but not all, of these cases have been associated with the reduction of oral glucocorticoid therapy.

Risks of aspirin treatment. Aspirin, or acetylsalicylic acid, is a nonsteroidal anti-inflammatory drug primarily used to temporarily relieve fever and minor aches and pains due to: headache, colds, muscle pain, toothache, menstrual pain, and arthritis pain. In this study we will be using the generic form of Bayer Aspirin Regimen (81 mg) and Ecotrin (325 mg). Aspirin is FDA approved and will be open label throughout the entire study. **Visit 2** of the intervention study involves desensitization to aspirin followed by twice daily administration of aspirin at 650 mg, which the patients will then continue as part of their standard medical regimen. Aspirin is being used as both a provocative agent and a therapeutic. The risks of aspirin treatment after desensitization are described here, whereas the risks of the aspirin desensitization procedure appear below. Treatment of individuals with AERD with aspirin is an accepted approach and a standard of practice for individuals with AERD whose sinonasal disease cannot be adequately controlled with topical or systemic glucocorticoid therapy. The most common side effects of aspirin are bruising, gastrointestinal bleeding, cerebral hemorrhage, gastric irritation, and tinnitus. In a study of aspirin at 650 mg twice daily as a long-term (1 year) treatment for AERD, 14% of 172 patients discontinued aspirin due to side effects, and 70% had a clinical benefit.[11]

Risks of corticosteroids. Virtually all subjects will have been on inhaled corticosteroids prior to enrollment in the study, and some will have been maintained on chronic oral steroids. Corticosteroid dosing will not be changed for this study. Nonetheless, subjects will be informed that when taken at high doses for extended periods, inhaled corticosteroids can produce hoarseness, sore throat, and thrush, as well as cause adrenal gland suppression, weight gain, bruising of the skin, and diabetes. Inhaled corticosteroids have also been associated with reduced growth velocity in children, but subjects in our study will all be age 18 and over.

5.4. Risks of Study Procedures

Risks of aspirin desensitization procedure. All individuals with AERD will experience a clinical reaction to aspirin, most often at a dose of 81 mg or below. By using the modified Scripps Institute protocol,[32] limiting the study to individuals with stable asthma and no history of life-threatening reaction to COX inhibitors, and administering montelukast to all individuals undergoing the challenge, the procedure can safely be done in an ambulatory setting and is routinely performed in the Allergy Clinic at the BWH. To ensure safety of the challenge, vital signs will be obtained every 90 minutes, and patients are instructed to report any of the following symptoms; cough, dyspnea, chest tightness, rhinorrhea, congestion, sneeze, ocular pruritus and discharge. Spirometry is repeated before each dose, or at the time symptoms are reported. A decrease in pre-challenge FEV_1 of 15% or more is considered indicative of a positive lower respiratory tract reaction. In our experience, ~60% of individuals with AERD who are treated with montelukast develop airflow obstruction of this magnitude, while the remainder experience a reaction confined to the sinonasal tract. In addition to respiratory symptoms, occasionally extrapulmonary symptoms occur as well, which can include gastrointestinal manifestations (abdominal discomfort, nausea, vomiting, or diarrhea) and skin manifestations (flushing, itching, and rash). Systemic reactions that involve the cardiovascular system are very rare in this selected population.

Injectable adrenalin, oxygen, and resuscitation equipment are present in the ARC in the unlikely event of a systemic reaction, as are physicians skilled in resuscitation.

Risks of ACQ, SNOT-22, and TNSS questionnaires. There are no risks associated with questionnaires.

Risk of blood draw. Risks associated with drawing blood include some pain when the needle is inserted. There is a small risk of bruising and/or infection at the place where the needle enters the arm. Some people may experience lightheadedness, nausea or fainting. It is possible to develop an infection, but this is rare and can be treated.

Risk of spirometry. Occasionally, individuals may develop a slight dizzy feeling and/or temporary cough and/or chest discomfort when performing breathing tests. These tests are used in hundreds of laboratories throughout the world on a daily basis without harmful effects.

Risks of Exhaled Nitric Oxide (FeNO). There are no known risked for exhaled nitric oxide collection.

Nasal fluid and cell collection. The nasal procedures that we will use to collect fluid and cells from the nose may be uncomfortable. When using a nasal sponge, the absorbent cotton material will increase in size with absorption of nasal discharge and may result in transient blockage of the nostrils or sensation of fullness or pressure. Local irritation of the nostril is possible which could include blood-tinged discharge that is expected to resolve on its own. To minimize the possibility of inducing blood-tinged discharge, we will alternate which nostril is used for nasal sample collection. Risk for infection will be minimized by using sterile absorbent material for each collection. Rinsing the nose with saline solution may result in accidental swallowing of the saline solution and brushing the inside of the nose may cause minor local bleeding.

5.5. Potential Benefits

Most subjects are expected to benefit from the desensitization and aspirin treatment following **Visit 2** of the study. There is a small potential benefit to individual subjects while taking ifetroban if it improves chronic symptoms or decrease the severity of response to aspirin challenge. If TP receptor antagonism does block features of the reaction to aspirin or improves symptomatic control of AERD, it would support the use of ifetroban or other TP receptor antagonists as potential therapeutic agents in AERD. Thus, the studies should shed light on how to improve therapy for AERD and better understand how these therapies work.

The risks associated with the treatments in this study are identifiable and small. There is extensive experience with ifetroban, and the brief period during which individuals are being treated with both ifetroban and aspirin are not likely to substantially increase the risk of bleeding. Furthermore, the risk of severe reactions to aspirin challenges are low, and such reactions can be readily managed in the study setting.

6. Investigational Agent /Device/Intervention

6.1. Investigational Agents/Devices/Interventions

6.1.1. Investigational Agent #1
Ifetroban: Cumberland Pharmaceuticals

6.1.1.1. Formulation, Packaging, and Labeling

Description of the Formulation: Ifetroban capsules are formulated as a dry powder blend and filled into hard gelatin capsules. The formulation consists of Ifetroban, mannitol, microcrystalline cellulose,

crospovidone, magnesium oxide, colloidal silicon dioxide, and magnesium stearate. Capsules are filled into high density polyethylene bottles and sealed with screw-cap closures.

Stability Characteristics of the Formulation: Ifetroban capsules are part of an ongoing stability study to support long term use in clinical studies. Available data suggest the capsules will be stable for at least 24 months.

6.1.1.2. Dosage, Preparation, and Administration

Oral Ifetroban is supplied as a 50mg capsule (4 capsules will be provided for each 200mg dose) for oral administration and is taken once daily. It is stored at controlled room temperature.

6.1.2. Investigational Agent #2

Placebo: Cumberland Pharmaceuticals

6.1.2.1. Formulation, Packaging, and Labeling

Description of the Formulation: Placebo for ifetroban capsules are formulated as a dry powder blend filled into capsules. The formulation consists of microcrystalline cellulose, crospovidone, colloidal silicon dioxide, and magnesium stearate. Capsules are filled into high density polyethylene bottles and sealed with screw-cap closures.

6.1.2.2. Dosage, Preparation, and Administration

Placebo capsules will be supplied for oral administration and 4 capsules will be taken once daily. It is stored at controlled room temperature.

6.1.3. Investigational Agent #3

Aspirin

6.1.3.1. Formulation, Packaging, and Labeling

- Active ingredient: Aspirin
- Doses will range from 40 mg- 650 mg.
- Doses will be given in the form of yellow (81 mg) or orange (325 mg) tablets.
- Store aspirin between 20° and 25° C (68° and 77° F).
- Manufactured by Rugby Laboratories, Duluth, Georgia.

6.1.3.2. Dosage, Preparation, and Administration

Aspirin will be open label. We will increase the dose of aspirin from 40 mg to 325 mg during the course of a day. All aspirin will be taken by mouth and should be taken with plenty of water. We will obtain the aspirin for this study from the IDS pharmacy. They will count and dispense the correct amount of aspirin needed. For the 40 mg dose of aspirin, we will use ½ of a chewable 81 mg tablet of aspirin.

6.2. Drug Accountability

Under Title 21 of the Code of Federal Regulations (21CFR §312.62) the investigator will maintain adequate records of the disposition of the investigational agent, including the date and quantity of the drug received, to whom the drug was dispensed (participant-by-participant accounting), and a detailed accounting of any drug accidentally or deliberately destroyed.

Records for receipt, storage, use, and disposition will be maintained by the study site. A drug-dispensing log will be kept current for each participant. This log will contain the identification of each participant and the date and quantity of drug dispensed.

All records regarding the disposition of the investigational product will be available for inspection by NIAID.

Unused study drugs will be returned to the IDS pharmacy. Unused study drugs will only be re-used if they were never in the hands of the subject. Once the subject has received the drugs, any unused drugs will be destroyed on site.

6.3. Assessment of Participant Compliance with Investigational Agent

Subjects will be asked to bring back any remaining doses of montelukast at Visits 1 and 2, and ifetroban or placebo, at Visit 2. We will provide subjects with bottles for each medication. The number of pills in the bottles will be clearly labeled on the bottle at the time of dispensation. We will also provide subjects with medication diary cards to fill out at home where they will write the number of study medication (ifetroban/placebo) and montelukast pills taken daily.

6.4. Toxicity Prevention and Management

No modifications are permitted.

6.5. Premature Discontinuation of Investigational Agent

Study therapy may be prematurely discontinued for any participant for any of the following reasons:

- A subject has more than one protocol-defined asthma exacerbation (defined as the development of an increase in symptoms of cough, chest tightness, or wheezing [independently of the symptoms anticipated to occur as a result of the aspirin challenge] requiring treatment with oral glucocorticoids. For those subjects maintained with a stable oral glucocorticoid dose, the definition will be an increase of ≥10 mg or a doubling of dose, whichever is less)
- The subject experiences gastrointestinal bleeding
- The subject becomes pregnant

Study therapy may also be prematurely discontinued for any participant if the investigator believes that the study treatment is no longer in the best interest of the participant. Subjects that must discontinue the investigational agent will come in for a final visit with a study physician.

7. Other Medications

7.1. Concomitant Medications

7.1.1. Protocol-mandated

Montelukast: Montelukast protects the lower airways from severe reactions in patients undergoing aspirin desensitization and thus increases the safety of aspirin challenges and desensitizations. It is the standard of care to use montelukast as a pre-treatment for patients with AERD undergoing a planned aspirin desensitization, and therefore all participants will be prescribed montelukast 10 mg daily for the duration of the study.

7.1.2. Other permitted concomitant medications

- **Inhaled, oral or nasal corticosteroids:** Participants may enter the trial on such medications based on the underlying condition. No modifications will be made with the exception of a temporary increase in the dose of oral corticosteroids if worsening asthma requires such an intervention. For those patients who require daily oral steroids for their standard maintenance regimen, they must be on no more than a daily dose of 10mg prednisone or equivalent for their standard daily therapy to be considered for inclusion.
- **Inhaled long acting beta-adrenergic agonists and inhaled ipratropium:** participants may enter the trial on such medications based on the underlying condition. No modifications will be made in the course of the trial.
- **Inhaled short acting beta-adrenergic agonists (PRN use):** participants may enter the trial on such medications based on the underlying condition. No modifications will be made in the course of the trial.

7.2. Prophylactic Medications

N/A

7.3. Prohibited Medications

- **Zileuton.** Subjects who were previously taking zileuton will discontinue it at the Screening Visit so as not to interfere with cysLT production and the accurate assessment of clinical symptoms occurring during the aspirin desensitization. A telephone encounter **(Phone Call 1)** 1 week after the Screening Visit will ensure safety and confirm stable asthma for those patients who were asked to discontinue zileuton. Zileuton may be used as a rescue medication during the aspirin desensitization procedure, but the subject must be free of zileuton for at least 3 weeks preceding each Study Visit.
- **Anticoagulants.** Use of warfarin or any other antiplatelet or anticoagulant medications will be prohibited.
- **Beta-blockers.** Due to the risk of bronchospasm associated with beta blockers, current use of any oral beta blocker will be prohibited.
- **NSAIDs.** The use of any additional non-steroidal anti-inflammatory drugs (NSAIDs), except the aspirin dosing as detailed for the study, will be prohibited throughout their participation in the study.
- **Biologics.** The use of any biologics is prohibited in the 120 days prior to Visit 1, and throughout the study.

7.4. Rescue Medications

The following medications can be used during the aspirin desensitization at Visit 2, for patient safety and/or comfort. Only albuterol and ipratropium may be used during the designated 3-hour period of observation following the onset of reaction symptoms. The remaining medications may only be provided for patient comfort after the 3-hour period of observation has concluded.

- **Albuterol.** 90 mcg/puff of MDI albuterol (up to 8 puffs per administration), a total of 3 administrations and 2.5mg of nebulized albuterol may be used as rescue inhalation treatment during the aspirin challenge/desensitization procedures, if bronchospasm occurs.
- **Ipratropium.** 0.5 mg/vial of ipratropium may be used during the aspirin challenge/desensitization procedures, if needed for patient comfort, to relieve any ongoing symptoms of reaction to aspirin if albuterol does not suffice.
- **Zileuton (Zyflo CR).** 1200 mg PO x1-2 may be given for patient comfort due to upper or lower respiratory symptoms, swelling, skin changes, or gastrointestinal discomfort.

- **Prednisone.** 20-50mg PO x1 may be given for patient comfort due to upper or lower respiratory symptoms, swelling, skin changes, or gastrointestinal discomfort.
- **Ondansetron.** 4-8 mg ODT tablet x1 may be given PO for patient comfort due to nausea, vomiting, or gastrointestinal discomfort.
- **Diphenhydramine.** 25 mg PO x1 may be given for patient comfort due to skin changes, itching, congestion, or rhinorrhea.

8. Study Procedures

8.1. Enrollment

Our study population will consist of individuals with suspected AERD referred to the Brigham and Women's Hospital (BWH) Drug Desensitization Program for diagnostic evaluation and potential aspirin challenge/desensitization. Patients seen in evaluation for suspected AERD in either the Allergy or Pulmonary Clinics at BWH will be identified by their allergist or pulmonologist, and if interest is expressed in aspirin challenge/desensitization and participation in the study, will be offered the opportunity to take home the Consent Form and call back if they wish to participate.

As several of the investigators conducting this study are recognized as specialists in the field of aspirin challenge/desensitization and management of patients with AERD, it is likely that a high proportion of patients with AERD will be identified from within their own clinical practice and referral base at BWH. In order to minimize the possibility that these patients will feel obligated to participate because it is their own physician who is asking, those investigators will initially present the study and offer a Consent Form to take home, and then ask a physician colleague or study coordinator to re-contact the potential study participant.

The research study will be explained in lay terms to each potential research participant. The potential participant will sign an informed consent form before undergoing any study procedures. Once the participant consents to the study and signs the informed consent, the participant is considered enrolled in the study and will be assigned a unique participant number.

8.2. Screening/Baseline Visit

Screening Visit The purpose of the screening visit is to confirm eligibility to continue in the study.

The following procedures, assessments, and laboratory measures will be conducted to determine participant eligibility:

1. A physical exam
2. Spirometry to assess lung function
3. Lab work (urine pregnancy, liver enzymes (AST and ALT), and creatinine level)
4. Assessment of asthma control (ACQ score, which evaluates asthma control over the proceeding 1 week)
5. Assessment of nasal symptoms (SNOT-22 score, which assesses nasal symptoms over the proceeding 2 weeks)
6. Baseline ECG

The labwork is typically completed within 24 hours of the blood draw. After the Screening Visit there is a 2-week Run-in Period in which subjects will begin taking montelukast 10mg daily (if not already on montelukast as part of their regular asthma care). A telephone encounter (Phone Call 1) 1 week later will ensure safety and confirm stable asthma.

8.3. Study Visits

Visit 1 After the 2-week Run-In period on montelukast, subjects will come into the ARC for their baseline visit (Visit 1). The following procedures, assessments, and laboratory measures will be conducted:

1. Interval history, physical exam, ACQ, SNOT-22, TNSS and spirometry will be recorded, along with FeNO.
2. Blood will be drawn for CBC/differential, and the cellular profiling and activation assays.
3. A urine sample will be collected for pregnancy and eicosanoid metabolites. Nasal lavage for cytokine and eicosanoid measurements and a nasal epithelial scraping sample for RNA extraction will be taken.
4. Subjects will be randomized to receive ifetroban (200 mg dose per day), or placebo for 4 weeks.

Subjects will take ifetroban or placebo daily for 4 weeks and will continue taking daily montelukast. There will be a telephone encounter **(Phone Call 2)** 1 week into this Treatment Period to ensure safety and confirm that chronic asthma symptoms have not worsened (as assessed by an ACQ-6 score).

Pharmacokinetic studies of ifebtroban have demonstrated that ifetroban absorption is lower, and maximum plasma concentration is lower, if the drug is taken following a meal. To ensure that absorption of the oral ifetroban is consistent, it is recommended that it should be taken 30 minutes or more prior to a meal. Therefore, we will request that patients take their daily ifetroban or placebo tablets first thing in the morning, at least 30 minutes before their breakfast.

Until institutional guidelines change, all subjects must obtain a negative COVID-19 test result within 72 hours prior to Visit 2. This is to ensure the safety of study staff during the pandemic due to aerosol-generating procedures that may occur at Visit 2. If the COVID-19 test comes back positive, the subject will be informed of their positive results and will be withdrawn from the study. They will receive a safety phone call one week later as follow-up.

Study staff will refer subjects to the current best PCR COVID test available advised by Infectious Disease.

Visit 2 After the 4-week treatment period, subjects will come into the ARC for **Visit 2**.

1. Interval history, physical exam, ACQ, SNOT-22, TNSS and spirometry will be recorded, along with FeNO.
2. Before aspirin is given, a urine sample will be collected for pregnancy and eicosanoid metabolites, and a nasal fluid and nasal epithelial scraping sample will be taken, along with a blood draw for CBC/differential and cellular assays.
3. Subjects will then undergo an oral aspirin desensitization procedure. They will receive an initial 40.5 mg dose of aspirin, and then every 90 minutes will be given increasing doses of 81, 162, and 325 mg aspirin.
4. Vital signs are obtained every 90 minutes during the aspirin challenge/desensitization.
5. If at any point the subject develops symptoms of a reaction, we will examine them and record the time of onset of reaction. The dose of reaction that induces an increase in TNSS of 2 or more points will be recorded as the provocative dose.
6. Following the onset of reaction, patients will be observed for a 3-hour period, during which time no more aspirin doses will be given. TNSS will be recorded at the onset of reaction and again every 30 minutes during this 3-hour period after reaction.
7. Pulmonary function testing is repeated before each dose and at the onset of reaction and if it remains within 85% of their pre-challenge FEV_1, it will be repeated every 90 minutes during the 3-hour period after reaction. If the FEV_1 falls by 15% or more from their morning pre-challenge FEV_1, they will be treated with

MDI albuterol (up to 8 puffs per administration), followed by nebulized albuterol if needed and FEV_1 will be repeated every 30 minutes until it has returned to within 85% of their morning pre-challenge FEV_1.

8. No medications (except albuterol and ipratropium) will be used for relief of symptoms during the desensitization until the 3-hour period of observation following onset of reaction is completed, unless required for a patient's safety.

9. A blood sample will be collected 1 hour after the onset of reaction for CBC/differential, platelet activation assays, and platelet-leukocyte aggregate measurements. Urine and nasal fluid samples will be collected 90 minutes after the onset of reaction, or if there is no clinical reaction at all, will be collected 90 minutes after the 325mg dose of aspirin is given.

Upon completion of the 3-hour period of observation, the subject will receive the provocative dose for a second time followed by the next subsequent aspirin dose after 90 minute observation intervals. Once the subject has effectively tolerated, as determined by a study physician, the repeat provocative dose and one subsequent dose bringing the cumulative dose of aspirin ingested during the procedure to ≥325 mg, the subject will be discharged home 90 minutes after the last dose, and will be instructed to begin taking daily aspirin, 325mg twice daily for a week until the Phone Call 3, as is part of our standard-of-care for these patients.
Following the 3-hour period of observation, the rescue medications described in Section 7.4 may be used for patient comfort. A sufficient 2-week supply of aspirin will be provided for patients so that they have enough to have them continue daily aspirin through the 2-week follow-up phase.

Follow-up Phase (2 weeks): During the follow-up phase, safety will be assessed through a telephone interview (Phone Call 3) 1 week after **Visit 2** to recommend the patient increases their daily aspirin dose from 325mg twice daily to 650mg twice daily, and again through a telephone interview (Phone Call 4) 1 week after that dose increase to ensure that the patient is tolerating the 650mg twice daily aspirin therapy and to ensure that the patient has an appropriate follow-up visit scheduled with their primary provider within 2 months of initiating the daily aspirin therapy. In order to ensure patient safety and consistency, patients will be prescribed sufficient montelukast at the Screening Visit to have them continue daily montelukast through this follow-up phase.

8.4. Visit Windows

Study visits should take place within the time limits specified below: the designated visit windows *(i.e. +/- n days)* for each scheduled visit are also indicated on the Table of Events.

Table 3. Table of Events.

Screening Visit	Phone Call 1	Visit 1**	Phone Call 2	Visit 2	Follow-up: Phone Call 3	Follow-up: Phone Call 4
Week 0	Week 1 (±3 days)	Week 2 (±5 days)*	Week 3 (±3 days)	Week 6 (+10 days/- 5 days)	Week 7 (± 3 days)	Week 8 (±3 days)

*The run in period after the Screening Visit can be skipped for Visit 1 if the subject is already taking montelukast at the time of the Screening Visit, so that for patients already taking montelukast for at least 2 weeks prior to Screening, Visit 1 could occur as soon as 24 hours after Screening.

**A 6-week supply of ifetroban will be provided at Visit 1.

9. Mechanistic Assays

Assess the effect of TP receptor blockade in vivo on platelet activation in vivo. 20 -40µL of blood or platelet-rich plasma will be stained with Abs against CD61 and P-selectin. The percentages of P-selectin$^+$ events in the CD61$^+$ platelet-sized

gate will be determined. The changes in P-selectin$^+$ platelets will be correlated with the corresponding changes in urinary eicosanoids and nasal lavage eicosanoids.

Assess the effect of TP receptor blockade on platelet activation in vitro. Platelet rich plasma obtained at visit 1 and before the challenge at Visit 2 will be stimulated with LTC_4 or with U46619 for 30 min. Platelets will be monitored for activation, and platelet-free supernatants monitored for TXA_2 generation.

Determine the effect of TP receptor blockade on release of mediators derived from cell activation. Nasal lavage fluids will be collected once at Visit 1 and again prior to administration of aspirin at Visit 2 and then serially at Visit 2 during the reactions to aspirin, and will be monitored by ELISA for mediators derived from mast cell and platelet activation.

Monitor innate Type 2 cytokine expression. RNA from nasal scrapings obtained at Visits 1 and 2 (before challenge) will be subjected to qPCR analysis for expressions of IL-33 and TSLP. Nasal fluid IL-33 levels will be measured at baseline and during reactions.

Monitor activation of mast cells and their associated eicosanoids. Total tryptase concentrations in nasal fluid and plasma/serum will be measured by ELISA (performed at Virginia Commonwealth University on a fee-for service basis). Urinary PG metabolites will be measured by GC-MS and LTE_4 by LC-MS as in our previous studies,[12] and nasal eicosanoids will be measured by ELISA.

10. Biospecimen Storage

The following biospecimen types will be obtained with the intention to be analyzed within the context of this protocol, but in some cases, there may be excess sample volume left over after the specified analyses. In those cases, the excess volume would be stored in our long-term biorepository (Core C) as detailed in the AADCRC overall proposal.

- Nasal fluid
- Nasal cells
- Urine
- Plasma
- Serum

Sample storage data will be accessible only to members of the AADCRC projects at BWH, and the BWH Asthma Research Center via clinical sample management software. Before patient visits, anticipated samples will be entered into the database and associated with the patient ID and the date and number of the visit so that labels for sample containers can be printed and applied. When samples are received, the entries will be updated to reflect the actual type and number of samples obtained, any aliquots of samples to be made for storage purposes will be accounted for, labels will be printed for the aliquot tubes, and space in a dedicated -80°C freezer will be assigned. This process will permit tracking of the history of all samples, as well as multi-parameter searches to identify and locate samples with the characteristics and thus minimize temperature fluctuations in the freezer when samples are sought.

11. Criteria for Participant and Study Completion and Premature Study Termination

11.1. Participant Completion

After completing Visit 2, the subjects will have completed the study.

11.2. Participant Stopping Rules and Withdrawal Criteria

Participants may be prematurely terminated from the study for the following reasons:

1. The participant elects to withdraw consent from all future study activities, including follow-up.
2. The participant is "lost to follow-up" (i.e., no further follow-up is possible because attempts to reestablish contact with the participant have failed).
3. The participant dies.
4. The Investigator no longer believes participation is in the best interest of the participant.
5. A subject has more than one protocol-defined asthma exacerbation (defined as the development of an increase in symptoms of cough, chest tightness, or wheezing [independently of the symptoms anticipated to occur as a result of the aspirin challenge] requiring treatment with oral glucocorticoids. For those subjects maintained with a stable oral glucocorticoid dose, the definition will be an increase of ≥10 mg or a doubling of dose, whichever is less)
6. The subject experience gastrointestinal bleeding
7. The subject becomes pregnant

11.3. Participant Replacement

Additional participants will be recruited if a participants withdraw or are withdrawn if the termination occurs prior to receiving the first dose of the study medication (ifetroban or placebo).

11.4. Follow-up after Early Study Withdrawal

If a subject needs to discontinue any of the investigational drugs prior to the end of the study, we will ask him/her to come in for one final visit. During this visit we will ask them to return all unused medication, have one final blood draw (to make sure their complete blood count (CBC) is normal), and one final pregnancy test (if applicable). If the subject does not return for this final visit, a study investigator will attempt to speak to the subject by telephone, and if unreachable at their preferred contact number, a clear message regarding the importance of follow-up and study investigator contact information will be left. If a subject experiences an adverse event that results in discontinuation from the study, we will follow the subject until the event is resolved or until the subject is discharged to alternate care.

11.5. Study Stopping Rules

The study may be prematurely terminated for the following reasons:

The Study PI or ISM may terminate this study at any time. Reasons for termination may include, but are not limited to the incidence or severity of AEs in this study indicating a potential health hazard to subjects or unsatisfactory subject enrollment. Any serious and/or persistent noncompliance by the investigator with the protocol, the clinical research agreement, the Form FDA 1572, or other local applicable regulatory guidelines in conducting the study may also be grounds for termination of the study. The PI will promptly inform all other investigators conducting the study if the study is suspended or terminated for safety reasons and will also inform the regulatory authorities of the suspension or termination of the study and the reason(s) for the action.

Study enrollment, investigational drug, and study procedures will be suspended pending expedited review of all pertinent data by the IRB and the NIAID, if any one of the following occurs:

1. If any death occurs that is designated as related to ifetroban or to a study procedure

2. If 3 AERD enrolled trial participants experience serious non-fatal AEs related to aspirin desensitization, or if 2 AERD enrolled participants experience serious non-fatal AEs related to ifetroban/placebo, or to another study procedure.

12. Safety Monitoring and Reporting

12.1 Overview

This section defines the types of safety data that will be collected under this protocol and outlines the procedures for appropriately collecting, grading, recording, and reporting those data. Adverse events that are classified as serious according to the definition of health authorities must be reported promptly (per Section 12.5, *Reporting of Serious Adverse Events and Adverse Events*) to the sponsor DAIT/NIAID. Appropriate notifications will also be made to site principal investigators, Institutional Review Boards (IRBs), and health authorities.

Information in this section complies with *ICH Guideline E2A: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, ICH Guideline E-6: Guideline for Good Clinical Practice*, 21CFR Parts 312 and 320, and applies the standards set forth in the National Cancer Institute (NCI), Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0: http://ctep.cancer.gov/reporting/ctc.html.

12.2 Definitions

12.2.1 Adverse Event (AE)

Any untoward or unfavorable medical occurrence associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research (modified from the definition of adverse events in the 1996 International Conference on Harmonization E-6 Guidelines for Good Clinical Practice) (from OHRP "Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events (1/15/07)" http://www.hhs.gov/ohrp/policy/advevntguid.html#Q2)

For this study, an adverse event will include any untoward or unfavorable medical occurrence associated with:

- **Study therapy regimen**:
    - Ifetroban: any AEs occurring during the treatment period after randomization and for 14 days after completion or discontinuation from the study.
    - Aspirin desensitization: any AEs occurring during the aspirin desensitization and for 14 days after completion or discontinuation from the study.
        - The aspirin challenge/desensitization procedures are expected to produce a set of aspirin-induced reaction symptoms, which can vary from patient-to-patient, and are listed in **Section 5.4 Risks of aspirin desensitization procedure**. These common and transient aspirin-induced reaction symptoms will not be reported as AEs. However, if any of the following events occur that are associated with the aspirin-induced reaction during the desensitization, they WILL be reported as AEs:
            1. Aspirin-induced bronchoconstriction with a fall in FEV1 of >50% from that morning's baseline value.
            2. Aspirin-induced symptomatic hypotension (fall in SBP of 20% or more from that morning's baseline value).

3. Any aspirin-induced reaction that produces symptoms severe enough to warrant the use of injectable epinephrine (including, but not limited to, angioedema of the respiratory tract and prolonged hypotension), as deemed medically necessary by the treating study physician.

4. Any aspirin-induced reaction that produces symptoms severe enough to warrant transfer of the patient to the Emergency Department for monitoring, as deemed medically necessary by the treating study physician.

- **Study mandated procedures**: Blood draw: Any AE occurring 24 hours after blood collection. Nasal sample collection: Any AE occurring 24 hours after procedure.

12.2.1.1 Suspected Adverse Reaction (SAR)

Any adverse event for which there is a reasonable possibility that the investigational drug or investigational study therapy regimen caused the adverse event. For the purposes of safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug (21 CFR 312.32(a)).

12.2.2 Unexpected Adverse Event

An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the *Investigator Brochure or package insert* or is not listed at the specificity, severity or rate of occurrence that has been observed; or is not consistent with the risk information described in the general investigational plan or elsewhere in the IND. Any event not listed as a known risk for the aspirin challenge will be considered an unexpected adverse event.

12.2.3 Serious Adverse Event (SAE)

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or Sponsor or DAIT/NIAID, it results in any of the following outcomes (21 CFR 312.32(a)):

1. Death.
2. A life-threatening event: An AE or SAR is considered "life-threatening" if, in the view of either the investigator or Sponsor or DAIT/NIAID, its occurrence places the subject at immediate risk of death. It does not include an AE or SAR that, had it occurred in a more severe form, might have caused death.
3. Inpatient hospitalization or prolongation of existing hospitalization.
4. Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
5. Congenital anomaly or birth defect.
6. Important medical events that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

Elective hospitalizations or hospital admissions for the purpose of conduct of protocol mandated procedures are not to be reported as an SAE unless hospitalization is prolonged due to complications.

12.3 Grading and Attribution of Adverse Events

12.3.1 Grading Criteria

The study site will grade the severity of adverse events experienced by the study subjects according to the criteria set forth in the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. This document (referred to herein as the NCI-CTCAE manual) provides a common language to

describe levels of severity, to analyze and interpret data, and to articulate the clinical significance of all adverse events. The NCI-CTCAE has been reviewed by the*, Principal Investigator,* and has been deemed appropriate for the subject population to be studied in this protocol.

Adverse events will be graded on a scale from 1 to 5 according to the following standards in the NCI-CTCAE manual:

Grade 1 = mild adverse event.

Grade 2 = moderate adverse event.

Grade 3 = severe and undesirable adverse event.

Grade 4 = life-threatening or disabling adverse event.

Grade 5 = death.

Events grade 2 or higher will be recorded on the appropriate AE case paper CRF report form for this study.

For grading an abnormal value or result of a clinical or laboratory evaluation (including, but not limited to, a radiograph, an ultrasound, an electrocardiogram etc.), a treatment-emergent adverse event is defined as an increase in grade from baseline or from the last post-baseline value that doesn't meet grading criteria. Changes in grade from screening to baseline will also be recorded as adverse events, but are not treatment-emergent. If a specific event or result from a given clinical or laboratory evaluation is not included in the NCI-CTCAE manual, then an abnormal result would be considered an adverse event if changes in therapy or monitoring are implemented as a result of the event/result.

12.3.2 Attribution Definitions

The relationship, or attribution, of an adverse event to the study therapy regimen or study procedure(s) will initially be determined by the site investigator and recorded on the appropriate AE paper case report form (AE/SAE paper CRF). Final determination of attribution for safety reporting will be determined by DAIT/NIAID. The relationship of an adverse event to study therapy regimen or procedures will be determined using the descriptors and definitions provided in Table 12.3.2.

For additional information and a printable version of the NCI-CTCAE manual, consult the NCI-CTCAE web site: http://ctep.cancer.gov/reporting/ctc.html.

Table 12.3.2 Attribution of Adverse Events

Code	Descriptor	Definition (guidelines)
UNRELATED CATEGORY		
1	Unrelated	The adverse event is clearly not related to study. The event is completely related to an etiology other than the study product or study intervention (the alternative etiology must be documented in the study subject's medical record)
2	Unlikely	The adverse event is doubtfully related to study and likely to be related to factors other than study product or study intervention.
RELATED CATEGORIES		

3	Possible	The adverse event may be related to study. There is an association between the event and the administration of study product and there is a plausible mechanism for the event to be related to the study product; there may be also an alternative etiology, such as characteristics of the subject's clinical status and/or underlying disease
4	Probable	The adverse event is likely related to study. There is (1) an association between the event and the administration of study product or study intervention, (2) a plausible mechanism for the event to be related to the study product, and (3) the event could not be reasonably explained by known characteristics of the subject's clinical status and or an alternative etiology is not apparent
5	Definite	The adverse event is clearly related to study. There is (1) an association between the event and the administration of the study product or study intervention, (2) a plausible mechanism for the event to be related to the related to the study product, and (3) causes other than the study product have been ruled out and/or the event re-appeared on re-exposure to the study product

12.4 Collection and Recording of Adverse Events

12.4.1 Collection Period

Adverse events will be collected from the time of enrollment, until a subject completes study participation or until 14 days after he/she prematurely withdraws (without withdrawing consent) or is withdrawn from the study if the subject has received study medication or has undergone aspirin challenge.

12.4.2 Collecting Adverse Events

Adverse events (including SAEs) may be discovered through any of these methods:

- Observing the subject.
- Interviewing the subject with specific questions about whether there has been any change in health status.
- Receiving an unsolicited complaint from the subject.
- Notification through the hospital medical record
- In addition, an abnormal value or result from a clinical or laboratory evaluation can also indicate an adverse event, as defined in Section 12.3, *Grading and Attribution of Adverse Events.*

12.4.3 Recording Adverse Events

Throughout the study, the investigator will record adverse events and serious adverse events as described previously on the appropriate paper case report form (AE/SAE paper CRF) regardless of the relationship to study therapy regimen or study procedure.

Once recorded, an AE/SAE will be followed until it resolves with or without sequelae, or until the end of study participation, or until 14 days after the subject prematurely withdraws (without withdrawing consent)/or is withdrawn from the study, whichever occurs first.

12.5 Reporting of Serious Adverse Events and Adverse Events

12.5.1 Reporting of Serious Adverse Events to Sponsor (DAIT/NIAID)

This section describes the responsibilities of the site investigator to report serious adverse events to the sponsor via *email.* Timely reporting of adverse events is required by 21 CFR and ICH E6 guidelines.

Site investigators will report all serious adverse events to the sponsor in any of the "related" categories (see Section 12.2.3, *Serious Adverse Event)*, regardless of expectedness within 24 hours of discovering the event.

For serious adverse events, all requested information on the AE/SAE paper CRF will be provided. However, unavailable details of the event will not delay submission of the known information. As additional details become available, the AE/SAE paper CRF will be updated and submitted.

12.5.2 Reporting to Health Authority

After an adverse event requiring 24-hour reporting (per Section 12.5.1, *Reporting of Serious Adverse Events to Sponsor*) is submitted by the site investigator and assessed by DAIT/NIAID, there are two options for DAIT/NIAID to report the adverse event to the appropriate health authorities:

12.5.2.1 Annual Reporting

DAIT/NIAID will include in the annual study report to health authorities all adverse events classified as:

- Serious, expected, suspected adverse reactions (see Section 12.2.1.1, *Suspected Adverse Reaction,* and Section 12.2.2, *Unexpected Adverse Event*).
- Serious and not a suspected adverse reaction (see Section 12.2.2, *Suspected Adverse Reaction*).
- Pregnancies.

Note that all adverse events (not just those requiring 24-hour reporting) will be reported in the Annual DSMB Report.

12.5.2.2 Expedited Safety Reporting

This option, with 2 possible categories, applies if the adverse event is classified as one of the following:

Category 1: **Serious and unexpected suspected adverse reaction** [**SUSAR]** (see Section 12.2.1.1, *Suspected Adverse Reaction* and Section 12.2, *Unexpected Adverse Event* and 21 CFR 312.32(c)(1)i).

The sponsor shall report any suspected adverse reaction that is both serious and unexpected. The sponsor shall report an adverse event as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the study drug and the adverse event, such as:

1. A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, or Stevens-Johnson Syndrome);

2. One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g., tendon rupture);
3. An aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group.

Category 2: **Any findings from studies that suggests a significant human risk**

The sponsor shall report any findings from other epidemiological studies, analyses of adverse events within the current study or pooled analysis across clinical studies or animal or *in vitro* testing (e.g. mutagenicity, teratogenicity, carcinogenicity) that suggest a significant risk in humans exposed to the drug that would result in a safety-related change in the protocol, informed consent, investigator brochure or package insert or other aspects of the overall conduct of the study.

DAIT/NIAID shall notify the FDA and all participating investigators of *expedited Safety* within 15 calendar days; unexpected fatal or immediately life-threatening suspected adverse reaction(s) shall be reported as soon as possible or within 7 calendar days.

12.5.3 Reporting of Adverse Events to IRBs/IECs

All investigators shall report adverse events, including expedited reports, in a timely fashion to their respective IRBs/IECs in accordance with applicable regulations and guidelines. All *Safety Reports to the FDA* shall be distributed by *DAIT/NIAID* or designee to all participating institutions for site IRB/IEC submission.

12.6 Pregnancy Reporting

The investigator shall be informed immediately of any pregnancy in a study subject or a partner of a study subject. A pregnant subject shall be instructed to stop taking study medication. The investigator shall counsel the subject and discuss the risks of continuing with the pregnancy and the possible effects on the fetus. Monitoring by phone call of the pregnant subject shall continue until one month after the conclusion of the pregnancy.

The investigator shall report to the DAIT/NIAID all pregnancies within 1 business day of becoming aware of the event using the Pregnancy paper CRF. All pregnancies identified during the study shall be followed to conclusion and the outcome of each must be reported. The Pregnancy paper CRF shall be updated and submitted to the DAIT/NIAID when details about the outcome are available. When possible, similar information shall be obtained for a pregnancy occurring in a partner of a study subject.

Information requested about the delivery shall include:

- Gestational age at delivery
- Birth weight, length, and head circumference
- Gender
- Appearance, pulse, grimace, activity, and respiration (APGAR) score at 1 minute, 5 minutes, and 24 hours after birth, if available

- Any abnormalities.

All pregnancy complications that result in a congenital abnormality, birth defect, miscarriage, and medically indicated abortion - an SAE shall be submitted to the DAIT/NIAID using the SAE reporting procedures described above.

12.7 Reporting of Other Safety Information

An investigator shall promptly notify the site IRB as well as the DAIT/NIAID when an "unanticipated problem involving risks to subjects or others" is identified, which is not otherwise reportable as an adverse event.

12.8 Review of Safety Information

12.8.1 Medical Monitor Review

The DAIT/NIAID Medical Monitor shall receive monthly reports from the *Principal Investigator* compiling new and accumulating information on AEs, SAEs, and pregnancies recorded by the study site on appropriate paper CRFs.

In addition, the Medical Monitor shall review and make decisions on the disposition of the SAE and pregnancy reports received by the *Principal Investigator* (See *Reporting of Serious Adverse Events to Sponsor*, and *Pregnancy Reporting*).

12.8.2 ISM Review

12.8.2.1 Planned ISM Reviews

The Independent Safety Monitor (ISM) is a physician who is independent from the study team and will, at minimum, review all SAEs to assess for possible changes to the overall risk of the study. This person will be expected to communicate with the PI and the NIAID Medical Officer regarding any safety issues and may be requested to review study safety documentation.

The ISM shall review safety data at least yearly, which will include, at a minimum, a listing of all reported AEs and SAEs.

12.8.2.2 *Ad hoc* ISM Reviews

In addition to the pre-scheduled yearly data reviews and planned safety monitoring, the ISM may be called upon for *ad hoc* reviews. The ISM will review any event that potentially impacts safety at the request of the PI or DAIT/NIAID. In addition, the following events will trigger an *ad hoc* comprehensive safety review by the ISM:

- Any death that occurs in the study, which is possibly or definitely related to study treatment regimen.
- The occurrence of a Grade 3 or higher related and unexpected SAE in 3 or more of the study participants who have received a study treatment.

After review of the data, the ISM will make recommendations regarding study conduct and/or continuation.

12.8.3 DSMB Review

12.8.3.1 Planned DSMB Reviews

The Data and Safety Monitoring Board (DSMB) shall review safety data at least yearly during planned DSMB Data Review Meetings. Data for the planned safety reviews will include, at a minimum, a listing of all reported AEs and SAEs.

The DSMB will be informed of an Expedited Safety Report in a timely manner. DSMB notification will occur as soon as site personnel are aware of the event but no later than 72 hours, which aligns with the requirements set forth by institutional guidelines.

12.8.3.2 *Ad hoc* DSMB Reviews

In addition to the pre-scheduled data reviews and planned safety monitoring, the DSMB may be called upon for *ad hoc* reviews. The DSMB will review any event that potentially impacts safety at the request of the protocol chair or DAIT/NIAID. In addition, the following events will trigger an *ad hoc* comprehensive DSMB Safety Review:

- Any death that occurs in the study, which is possibly or definitely related to study treatment regimen.
- The occurrence of a Grade 3 or higher related and unexpected SAE in 3 or more of the study participants who have received a study treatment.

After review of the data, the DSMB will make recommendations regarding study conduct and/or continuation.

12.8.3.2.1 Temporary Suspension of enrollment for *ad hoc* DSMB Safety Review

A temporary halt in enrollment will be implemented if an *ad hoc* DSMB safety review is required.

In the event that study enrollment temporarily halts, new participants will not be consented during the enrollment halt. However, subjects already enrolled and on investigational drug/placebo will continue on therapy, and any subjects in the Screening phase of the study will continue to undergo minimal risk procedures.

13. Statistical Considerations and Analytical Plan

13.1 Overview

This Project will determine the role of TP receptors in the pathophysiology of AERD. Using a double blinded, placebo controlled crossover trial of ifetroban, a potent and selective TP receptor antagonist, we will test the central hypothesis that TP receptor signaling promotes persistent eosinophilic respiratory inflammation, drives cysLT overproduction, facilitates release of innate type 2 cytokines downstream of cysLTs and platelets, and mediates bronchoconstriction in response to TXA_2 and PGD_2 released by mast cells during reactions to aspirin in AERD. As such, TP receptor blockade will interfere with both the cysLT-dependent and -independent features of AERD pathophysiology and interrupt a feed-forward loop that drives the disease.

13.2 Outcomes

The primary outcome is the calculated dose of aspirin that induces an increase in the Total Nasal Symptom Score (TNSS) of 2 from the baseline value, or "PD_2". The PD_2 will be calculated during the aspirin desensitization at Visit 2 as follows:

$$\text{inverselog}_{10}\left(\frac{\left(2-(\text{PrevTNSS}-\text{BaselineTNSS})\right)\times(\log_{10}\text{ProvocDose}-\log_{10}\text{PrevDose})}{(\text{MaxTNSS}-\text{BaselineTNSS})-(\text{PrevTNSS}-\text{BaselineTNSS})}+(\log_{10}\text{PrevDose})\right)$$

Where:

Baseline TNSS = TNSS score prior to administration of aspirin

PrevTNSS = TNSS score immediately previous to onset of aspirin reaction

MaxTNSS = Maximum TNSS score recorded during 3-hour observation period during aspirin reaction

ProvocDose = Dose of aspirin that provoked a reaction

PrevDose = Dose of aspirin that preceded the provocative dose

The secondary and exploratory outcomes are detailed in Sections 3.3 and 3.4 and involve the measurement of clinical outcomes and biologic levels as measured at Visit 1, Visit 2 baseline and Visit 2 during aspirin-induced reactions, compared between patients on placebo vs ifetroban.

13.3 Measures to Minimize Bias

We will use block randomization, ensuring that equal numbers of subjects are randomized to each group. For this two-arm balanced-design study, the randomization will consist of blocks of patients randomly assigned (allocation ratio of 1:1) to ifetroban or placebo. Matching capsules of ifetroban and placebo will be supplied by Cumberland Pharmaceuticals and provided to the BWH Investigational Drugs Services pharmacy (IDS) for storage and distribution. The IDS will conduct the randomization and keep records to maintain study blinding.

Laboratory analyses (flow cytometry, cellular assays, eicosanoid measurement, etc.) as required for any secondary and exploratory outcomes will also be performed in a blinded fashion, as along with the clinical staff, laboratory staff will also be blinded during the study.

13.4 Analysis Plan

13.4.1 Analysis Populations.

N/A

13.4.2 Primary Analysis of Primary Outcome

To power for a change in the PD_2, we will use a two-sided two-sample t-test for mean difference with unequal variance, comparing the difference between treatment with ifetroban and placebo. Based on our current internal clinical data, we estimate an average PD_2 of 60, with a standard deviation of 42. Assuming this standard deviation to remain true, with a sample size of 20 patients per treatment arm, we will have 83% power to detect a 3-fold shift in PD_2 (or an average an increase in PD_2 to 180 for patients on ifetroban, with a standard deviation of 170), at a 0.05 level of significance.

13.4.3 Supportive Analyses of the Primary Endpoint(s)/Outcome(s)

N/A

13.4.4 Analyses of Secondary and Other Endpoint(s)/Outcome(s)

Using a two-sided two-sample t-test for mean difference with unequal variance we will compare each secondary outcome (aspirin-induced fall in FEV_1, aspirin-induced peak urinary LTE_4 and serum/nasal tryptase) separately on treatment with ifetroban or placebo. Based on our current internal clinical data:

i. We estimate an average maximum aspirin-induced fall in FEV_1 of 14.6% with a standard deviation of 8.3. With 20 patients per treatment group, we will have 72% power to detect a 50% difference in the fall of FEV_1 at a 0.05 level of significance.

ii. We estimate an average aspirin-induced peak urinary LTE_4 of 6.0 ng/mg Cr with a standard deviation of 3.9. With 20 patients per treatment group, we will have 74% power to detect a difference of 2.4 ng/mg Cr (or a 40% decrease in the rise in LTE_4) at a 0.05 level of significance.

We will compare each outcome (ifetroban-induced changes in baseline FEV_1, asthma control (ACQ), nasal symptoms (SNOT-22), FeNO and baseline LTE_4) separately after 4 weeks of treatment with ifetroban or placebo using a two-sided two-sample t-test. Based on our current internal clinical baseline data of 25 patients with AERD:

iii. We estimate an average baseline FEV_1 of 92% predicted and a standard deviation of 9.8, we will have 78% power to detect a difference in FEV_1 of 6%, at a 0.05 level of significance.

iv. We estimate an average baseline ACQ of 0.64 and a standard deviation of 0.54, we will have 82% power to detect a difference of 0.35 points, at a 0.05 level of significance. A fall in ACQ of 0.5 points is consistent with clinically significant improvement.[33]

v. We estimate an average baseline SNOT-22 score of 38 and a standard deviation of 14, we will have 86% power to detect a difference of 9 points, at a 0.05 level of significance. A fall in SNOT-22 score of 8.9 is consistent with clinically significant improvement.[34]

We estimate an average baseline urinary LTE_4 of 0.37 ng/mg Cr and a standard deviation of 0.22, we will have 80% power to detect a difference of 0.14 ng/mg Cr (or a decrease in urinary LTE_4 of 30% from baseline, roughly half of the effect of zileuton,[35,36] at a 0.05 level of significance.

13.4.5 Analyses of Exploratory Endpoint(s)/Outcome(s)

Nasal fluid IL-33 and tryptase levels are expected to increase during aspirin-induced reactions and those increases will be compared between patients on ifetroban vs. placebo to determine if ifetroban treatment blunts the aspirin-induced increases. The IL-33 and tryptase levels will also be correlated to clinical symptoms (TNSS and fall in FEV1). We will measure the incremental increase in platelet or mast cell-derived chemokines in the nasal fluid during aspirin-induced reactions for patients on ifetroban vs. placebo and determine if those increases are blunted by ifetroban or correlate with the increase in nasal eicosanoids during reaction.

13.4.6 Descriptive Analyses

Summary of descriptive statistics for baseline and demographic characteristics will be provided for all enrolled participants. Demographic data will include age, race, sex, body weight, and height; these data will be presented in the following manner: Age, body weight, and height will be averaged per treatment group. Race and sex will be summarized as the number and percent of subjects in each category. Baseline control and severity of asthma will be provided as tabular summaries of average baseline ACQ score, average baseline FEV_1 as percent of predicted, and average baseline daily corticosteroid use.

The percent of participants who complete the study, losses to follow-up, time to lost to follow-up, and reasons for discontinuation (e.g., adverse events) will be presented.

13.5 Interim Analyses

N/A

13.5.1 Interim Analysis of Efficacy Data

13.5.2 Interim Analysis of Safety Data

13.5.3 Futility Analysis

13.6 Statistical Hypotheses

See sections 13.4.2 through 13.4.5 above for detailed comparisons.

13.7 Sample Size Considerations

Assuming that there will be a dropout rate of 10-20%, we will seek to recruit 50 individuals with suspected AERD from our new referrals to meet a target sample size of 40 to complete the study, with 20 in each treatment arm. We will enroll additional subjects if we have an unusually high dropout rate. As detailed in section 13.4.2, with this sample size of 20 patients per treatment arm, we will have 83% power to detect a 3-fold shift in PD_2 (or an average an increase in PD_2 to 180 for patients on ifetroban, with a standard deviation of 170), at a 0.05 level of significance.

13. Identification and Access to Source Data

13.1. Source Data

The Principal Investigator will keep accurate records to ensure that the conduct of the study is fully documented. Data derived from source documents will be transferred to protocol-specific CRFs. Hard copy results of the following clinical evaluations and clinical laboratory evaluations will be maintained in the participant's protocol-specific binder, housed at the Asthma Research Center:

- Patient medical histories, concomitant medications, adverse event forms (results written onto CRF)
- CBC/differential (printed copy)
- PFTs (printed copy)
- FeNO (results written onto CRF by coordinator/investigator)
- Pregnancy test (results written onto CRF by coordinator/investigator)
- Physical exam (results written onto CRF by coordinator/investigator)
- Patient questionnaires (results written onto CRF by patient)
- Details of which biologic specimens collected at each visit (written onto CRF by coordinator/investigator)

The applicable clinical study data will be transferred to a password-secured REDCap database on a dedicated server.

Data derived from research laboratory evaluations (flow cytometry, eicosanoid and cytokine levels, cellular assays) will be stored as a hard copy (as applicable) within laboratory notebooks, or within the appropriate assay-specific software program as required for each type of analysis.

13.2. Access to Source Data

The site investigators and site staff will make all source data available to the DAIT/NIAID, as well as to relevant health authorities at Cumberland Pharmaceuticals.

14. Protocol Deviations

14.1. Protocol Deviation Definitions

Protocol Deviation – The investigators and site staff will conduct the study in accordance to the protocol; no deviations from the protocol are permitted. Any change, divergence, or departure from the study design or procedures constitutes a protocol deviation. As a result of any deviation, corrective actions will be developed by the site and implemented promptly.

Major Protocol Deviation (Protocol Violation) - A Protocol Violation is a deviation from the IRB approved protocol that may affect the subject's rights, safety, or well-being and/or the completeness, accuracy and reliability of the study data. In addition, protocol violations include willful or knowing breaches of human subject protection regulations, or policies, any action that is inconsistent with the NIH Human Research Protection Program's research, medical, and ethical principles, and a serious or continuing noncompliance with federal, state, local or institutional human subject protection regulations, policies, or procedures.

Non-Major Protocol Deviation - A non-major protocol deviation is any change, divergence, or departure from the study design or procedures of a research protocol that does not have a major impact on the subject's rights, safety or well-being, or the completeness, accuracy and reliability of the study data.

14.2. Reporting and Managing Protocol Deviations

The study site principal investigator has the responsibility to identify, document and report protocol deviations as directed by the study Sponsor. However, protocol deviations may also be identified during site monitoring visits or during other forms of study conduct review.

Upon determination that a protocol deviation has occurred, the study staff will a) notify the site Principal Investigator, b) notify the NIAID Project Manager, and c) will complete a Protocol Deviation form (See Appendix). NIAID may request discussion with the Principal Investigator and the Independent Safety Monitor to determine the effect of the protocol deviation on the study participant and his/her further study participation, the effect of the protocol deviation on the overall study and corrective actions. The Principal Investigator will complete and sign the Protocol Deviation form (See Appendix) and submit it to the NIAID Medical Officer and Project Manager, to the Independent Safety Monitor and to the site IRB, per IRB regulations. Major protocol deviations will be reported to the SMC by the NIAID Medical Officer.

It is the responsibility of the PI and study physician Co-Investigators to use continuous vigilance to identify and report deviations within 5 working days of identification of the protocol deviation, or within 5 working days of the scheduled protocol-required activity. All deviations will be promptly reported as above and will be addressed in study subject source documents. Deviations from the approved protocol are not allowed.

15. Ethical Considerations and Compliance with Good Clinical Practice

15.1. Statement of Compliance

This clinical study will be conducted using good clinical practice (GCP), as delineated in *Guidance for Industry: E6 Good Clinical Practice Consolidated Guidance*, and according to the criteria specified in this study protocol. Before study initiation, the protocol and the informed consent documents will be reviewed and approved by the IRB. Any amendments to the protocol or to the consent materials will also be approved by the IRB before they are implemented.

15.2. Informed Consent Process

The consent process will provide information about the study to a prospective participant and will allow adequate time for review and discussion prior to his/her decision. The principal investigator or designee listed on the *FDA 1572* will review the consent and answer questions. The prospective participant will be told that being in the trial is voluntary and that he or she may withdraw from the study at any time, for any reason. All participants (or their legally acceptable representative) will read, sign, and date a consent form before undergoing any study procedures. Consent materials will be presented in participants' primary language. A copy of the signed consent form will be given to the participant.

The consent process will be ongoing. The consent form will be revised when important new safety information is available, the protocol is amended, and/or new information becomes available that may affect participation in the study.

15.3. Privacy and Confidentiality

A participant's privacy and confidentiality will be respected throughout the study. Each participant will be assigned a unique identification number and these numbers rather than names will be used to collect, store, and report participant information. Site personnel will not transmit documents containing personal health identifiers (PHI) to the study sponsor or their representatives.

16. Publication Policy

The ICJME (International Committee of Medical Journal Editors) policy on the publication of study results will apply to this trial.

17. Appendix 1. Schedule of Events

Schedule of Events		Study Phase	Screen	Run-In	Treatment Period			Follow-up	
		Week	0	1	2	3	6	7	8
		Visit	V0	Phone Call 1	V1	Phone Call 2	V2	Phone Call 3	Phone Call 4
Procedures/Assessments									
Informed Consent, Verify eligibility			+						
Randomization (ifetroban/placebo)					+				
Physical Exam and vital signs			+		+		++		
Baseline symptoms (ACQ, SNOT-22)			+		+		+		
Spirometry			+		+		++		
Start montelukast			+						
Urine for:	Pregnancy test		+		+		+		
	Eicosanoids				+		++		
Blood for:	CBC/differential		+		+		+		
	Creatinine, LFTs		+						
	Platelet/WBC studies				+		++		
Nasal washings/scrape samples					+		++		
FeNO					+		+		
Aspirin desensitization							+		
Acute sinonasal symptoms (TNSS)							++		
Initiation of aspirin therapy							+		
Adverse event assessment				+	+	+	+	+	+

Appendix 2. Protocol Deviation Form

Subject ID: ___ ___ ___ ___ ___ ___ Date of Report: __ __ / __ __ / __ __ __ __ Subject Initials: ___ ___ ___

PROTOCOL DEVIATION REPORTING FORM

(one form per deviation)

1. Date Deviation occurred: __ __/__ __/ __ __ __ __

2. Date site Staff became aware of Deviation: __ __/__ __/ __ __ __ __

3. Description of Deviation:

_____

_____

_____*(attach continuation form, if needed)*

4. Circumstances explaining /contributing to the deviation:

_____

_____

_____*(attach continuation form, if needed)*

5. Effect of Deviation on subject's safety or risk from study participation:

No effect ☐

Safety concern or increased risk ☐ *AE or SAE form required B. Qualifies as "major deviation")*

Explain why the deviation has (or has not) an effect on subject's safety or risk from study participation. In case that deviation has an effect please provide extent of potential safety impact:

_____

_____

_____ *(attach continuation form, if needed)*

6. Effect of Deviation on the quality of study data:

No effect ☐

Potential effect on data quality ☐ *(Qualifies as "major deviation")*

Explain why deviation has (or has not) an effect on the quality of study data. In case that deviation has an effect please provide extent of potential effect on data quality:

_____

_____

_____*(attach continuation form, if needed)*

7. Major Deviation *(as determined by the NIAID Project Manager)* YES ☐ NO ☐

Subject ID: ___ ___ ___ ___ ___ ___ Date of Report: __ __ / __ __ / __ __ __ __ Subject Initials: ___ ___ ___

8. Corrective action(s) to resolve this Deviation:

_____

_____*(attach continuation form, if needed)*

9. Corrective action(s) to prevent similar occurrences in the future:

_____

_____

_____ *(attach continuation form, if needed)*

10. Participant will continue as a study subject: YES ☐ NO ☐

Justification:

_____

_____*(attach continuation form, if needed)*

11. Notifications

	Date Notified
NIAID Project Manager	
Independent Safety Monitor	
IRB	

_____

Name and Signature of Independent Safety Monitor *(if required)*

_____

Date Completed

_____

Name and Signature of Principal Investigator

_____

Date Completed

Participant ID: ___ ___ ___ ___ ___ ___ Date of Report: __ __ / __ __ / __ __ __ __

Participant's Initials: ___ ___ ___

PROTOCOL DEVIATION REPORTING FORM CONTINUATION PAGE

18. References

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