# CLINICAL STUDY PROTOCOL

# A Phase 2 Multicenter, Double-blind, Randomized, Placebo-Controlled Trial to Evaluate Oral Ifetroban in Subjects with Symptomatic Aspirin Exacerbated Respiratory Disease (AERD)

## Number: CPI-IFE-006

## Protocol Version

**Version Number:** Original Protocol
**Final:** 22 December 2016

**Amendment:** 01
**Revised Final:** 02 May 2018

### CONFIDENTIALITY STATEMENT

## RESPONSIBLE PERSONNEL

**Sponsor - Medically Responsible Person**

**Sponsor's Coordinating Office**

**Sponsor's Clinical Operations**

**Coordinating Investigator**

# 1 INVESTIGATOR'S STATEMENT

I have read and agree to the Protocol CPI-IFE-006, " A Phase 2 Multicenter, Double-blind, Randomized, Placebo-Controlled Trial to Evaluate Oral Ifetroban in Subjects with Symptomatic Aspirin Exacerbated Respiratory Disease (AERD), Amendment 01 dated 02 May 2018." I am aware of my responsibilities as an Investigator under the guidelines of Good Clinical Practice (GCP), local regulations (as applicable) and the study protocol. I agree to conduct the study according to these guidelines and to appropriately direct and assist the staff under my control, who will be involved in the study.

**Principal Investigator**

Signature:

_____ _____
Date of Signature

**Sponsor Signature**

Signature:

_____ _____
Date of Signature

Signature:

_____ _____
Date of Signature

# 2 SYNOPSIS

| **Name of Sponsor:** Cumberland Pharmaceuticals | **Name of Finished Product:** Ifetroban Capsules | **Name of Active Ingredient:** ifetroban |
|---|---|---|
| **Title of Study:** A Phase 2 Multicenter, Double-blind, Randomized, Placebo-Controlled Trial to Evaluate Oral Ifetroban in Subjects with Symptomatic Aspirin Exacerbated Respiratory Disease (AERD) | | |
| **Study Centers (Planned):** Eight | **Phase of Development:** II | |
| **Expected Study Duration (per subject):** Screening period (3 weeks) + Treatment period (8 weeks) + Post-treatment period (2 weeks) = 13 weeks | | |
| **Objectives:**<br>**Primary Study Objective**<br>• Determine the efficacy of ifetroban compared to placebo to improve sino-nasal symptoms and quality of life (QoL) using the Sino-nasal Outcome Test (SNOT) - 22 score in symptomatic AERD subjects.<br>**Secondary Study Objectives**<br>• Evaluate the effect of ifetroban on asthma symptoms by forced expiratory volume 1 (FEV1) compared to baseline.<br>• Assess nasal symptoms and QoL using the peak Nasal Inspiratory Flow Rate (PNIFR), University of Pennsylvania Smell Identification Test (UPSIT), fractional exhaled nitric oxide (FeNO), Asthma Control Questionnaire (ACQ) - 7 and Total Nasal Symptom Score (TNSS)<br>• Determine whether ifetroban reduces the frequency and severity of asthma exacerbations and chronic sinusitis as well as the frequency of rescue medication and antibiotic use.<br>• Evaluate the pharmacodynamic effects of TPr blockade on eicosanoids and eosinophil count | | |
| **Methodology:** This is a multicenter, randomized, double-blind, placebo-controlled study to evaluate the effect of 200 mg of oral ifetroban administered once daily for eight weeks. | | |
| **Number of subjects (planned):** A total of 76 AERD subjects will be randomized: 38 ifetroban, 38 placebo | | |

| **Name of Sponsor:** | **Name of Finished Product:** | **Name of Active Ingredient:** |
|---|---|---|
| Cumberland Pharmaceuticals | Ifetroban Capsules | ifetroban |

**Study Population – Main Selection Criteria**

**Inclusion criteria:**

1. History of physician-diagnosed asthma
2. History of nasal polyposis
3. History of at least **two** reactions to oral aspirin or other nonselective cyclooxygenase inhibitor with features of lower airway involvement (cough, chest tightness, wheezing, dyspnea) or one reaction that was life-threatening and required hospitalization, **or** a diagnosis of AERD by a physician-conducted challenge to aspirin in the last five years before starting treatment.
4. Stable asthma (post-bronchodilator FEV1 of ≥ 60%, no glucocorticoid burst for at least two weeks prior to starting treatment, no hospitalizations or emergency room visits for asthma at least three months prior to starting treatment and not on a dose >1000 µg fluticasone or equivalent daily).
5. ≥ 18 years of age
6. Exhibit symptomatic AERD within three weeks of starting treatment by demonstrating a score of at least 20 on the Sino-nasal Outcome Test (SNOT) – 22.

**Exclusion criteria:**

1. Current smoking, defined as daily tobacco smoking in the last six months and at least one instance of tobacco smoking in the last three months.
2. Current pregnancy or breastfeeding
3. Use of oral or systemic steroids (e.g. prednisone or equivalent) > 20 mg daily in the last four weeks before starting treatment.
4. Daily use of long-acting antihistamines in the last two weeks before starting treatment.
5. Less than 12 months of allergy shots (maintenance dose of allergy shots are allowed if treatment duration exceeds 12 months).
6. Any use of nonsteroidal anti-inflammatory drugs (NSAIDs) or any drug that inhibits the cyclooxygenase enzyme in the last two weeks before starting treatment.
7. History of bleeding diathesis or use of anticoagulant or antiplatelet drugs in the last two weeks before starting treatment.
8. Any immunosuppressive treatment including but not limited to methotrexate, cyclosporine, mycophenolate, tacrolimus, gold, penicillamine, sulfasalazine, hydroxychloroquine, azathioprine and cyclophosphamide in the last two weeks before starting treatment (maintenance dose of allergy shots are allowed if treatment duration exceeds 12 months). Biologics/immunotherapies such as Xolair or Nucala are permitted if duration exceeds three months.
9. Endoscopic sinus surgery / polypectomy within the past three months
10. Previously treated in a clinical trial with ifetroban within the past three months.
11. Previously treated with other investigational drugs within eight weeks or five half-lives, whichever is longer, before screening
12. Conditions/concomitant disease which make them unevaluable for the efficacy endpoints

**Investigational Medicinal Product (IMP), dose and mode of administration:**
Oral ifetroban capsules (200 mg)

**Duration of treatment:** eight weeks

| **Name of Sponsor:** Cumberland Pharmaceuticals | **Name of Finished Product:** Ifetroban Capsules | **Name of Active Ingredient:** ifetroban |
|---|---|---|
| **Reference therapy, dose and mode of administration:** Matching oral placebo capsules | | |
| **Endpoints:**<br>**Efficacy:** SNOT-22, ACQ-7, FEV1, UPSIT, FeNO, PNIFR and TNSS<br>**Safety, tolerability and other exploratory endpoints:** vital signs, adverse events (AE), physical examination, clinical laboratory tests and biomarkers. | | |
| **Sample Size:**<br>38 subjects per group will provide 90% power for the comparison of ifetroban and placebo with respect to the change from baseline in SNOT-22 scores at Week 8 (two-sided, level 0.05), assuming a common standard deviation of 16 and a true difference is 12.<br>**Randomization:**<br>Subjects will be randomized using a 1:1 randomization ratio for ifetroban 200 mg daily for eight weeks, or placebo daily for eight weeks.<br><br>**Analysis Population:**<br>All subjects who received at least one dose of study medication will be included in the Safety Population. All safety data, including AEs, laboratory parameter, vital signs, FEV1 and physical examinations, will be summarized for subjects in the Safety Population.<br><br>The Intent-To-Treat (ITT) Population will consist of all treated subjects with at least one post-baseline assessment of SNOT-22. The Per Protocol (PP) Population will consist of all subjects in the ITT population with no major protocol violations, including violation of inclusion or exclusion criteria or insufficient dosing. All efficacy analyses will be performed for both the ITT and PP Populations. Summary statistics will be presented for each corresponding analysis.<br><br>**Primary Analysis:**<br>The primary efficacy endpoint is the Change From Baseline (CFB) in SNOT-22 score and the primary analysis is the analysis of CFB in SNOT-22 at Week 8, using Analysis of Covariance (ANCOVA), with SNOT-22 at Baseline included as the only covariate.<br><br>**Secondary Analyses**<br>CFB in ACQ-7 and CFB in TNSS at Week 8 will be analyzed using ANCOVA, with the corresponding value at Baseline included as the only covariate. These variables, as well as CFB in SNOT-22, at Week 4 will also be analyzed as ancillary analyses.<br><br>Analyses of CFB for other continuous efficacy variables at Weeks 4 and 8 will be performed as ancillary analyses using ANCOVA with the corresponding value at Baseline included as the only covariate. Responder analyses, defined as any improvement in SNOT-22, ACQ-7, and TNSS (Yes or No) at Weeks 4 and 8 will be performed as ancillary analyses using the normal approximation to the binomial distribution, assuming unequal variances. | | |

# 3 TABLE OF CONTENTS

# 4 LIST OF ABBREVIATIONS

| Abbreviation | Definition |
|---|---|
| 5-LO | 5-Lipoxygenase |
| ACQ | Asthma Control Questionnaire |
| AE | Adverse Event/Experience |
| AERD | Aspirin Exacerbated Respiratory Disease |
| ANCOVA | Analysis of Covariance |
| AUC | Area Under the Curve |
| C | Celsius |
| CFB | Change From Baseline |
| CFR | Code of Federal Regulations |
| cm | Centimeter |
| $C_{max}$ | Maximum Plasma Concentration |
| COX | Cyclooxygenase |
| CRF | Case Report Form |
| CPI | Cumberland Pharmaceuticals Inc. |
| cysLT | Cysteinyl Leukotriene |
| CysLT1R | Cysteinyl Leukotriene 1 Receptor |
| ER | Emergency Room |
| F | Fahrenheit |
| FDA | Food and Drug Administration |
| FeNO | Fractional exhaled Nitric Oxide |
| FEV1 | Forced Expiratory Volume in 1 Second |
| GCP | Good Clinical Practice |
| ICH | International Conference on Harmonization |
| IEC | Independent Ethics Committee |
| IMP | Investigational Medicinal Product; synonymous with “study drug” |
| INR | International normalized ratio |
| IRB | Institutional Review Board |
| ITT | Intent-To-Treat |
| kg | Kilogram |
| L | Liter |
| $LTC_4$ | Leukotriene $C_4$ |
| $LTE_4$ | Leukotriene $E_4$ |
| MCID | Minimal Clinically Important Difference |
| MedDRA | Medical Dictionary for Regulatory Activities |

| Abbreviation | Definition |
|---|---|
| mg | Milligram |
| mL | Milliliter |
| NSAID | Nonsteroidal Anti-inflammatory Drug |
| PD | Pharmacodynamic |
| PG | Prostaglandin |
| $PGD_2$ | Prostaglandin $D_2$ |
| PNIFR | Peak Nasal Inspiratory Flow Rate |
| PP | Per Protocol |
| PRN | pro re nata (use when necessary) |
| PT | Prothrombin time |
| Ptges | PGE2 synthase |
| QoL | Quality of Life |
| SAE | Serious Adverse Event/Experience |
| SNOT-22 | Sino-nasal Outcome Test-22 |
| SOC | System Organ Class |
| TBXAS | Thromboxane A2 synthase |
| TEAE | Treatment Emergent Adverse Event |
| $T_{max}$ | Time of maximum plasma concentration |
| TNSS | Total Nasal Symptom Score |
| TPr | Thromboxane Prostanoid Receptor |
| TXA2 | Thromboxane A2 |
| UPSIT | University of Pennsylvania Smell Identification Test |

# 5 INTRODUCTION

This study is to be performed in accordance with the International Conference on Harmonization's (ICH) E6 guideline for Good Clinical Practice (GCP), the ethical principles that have their origin in the Declaration of Helsinki, Title 21 of the Code of Federal Regulations (CFR) Parts 50, 56 and 312.

## 5.1 Background Information

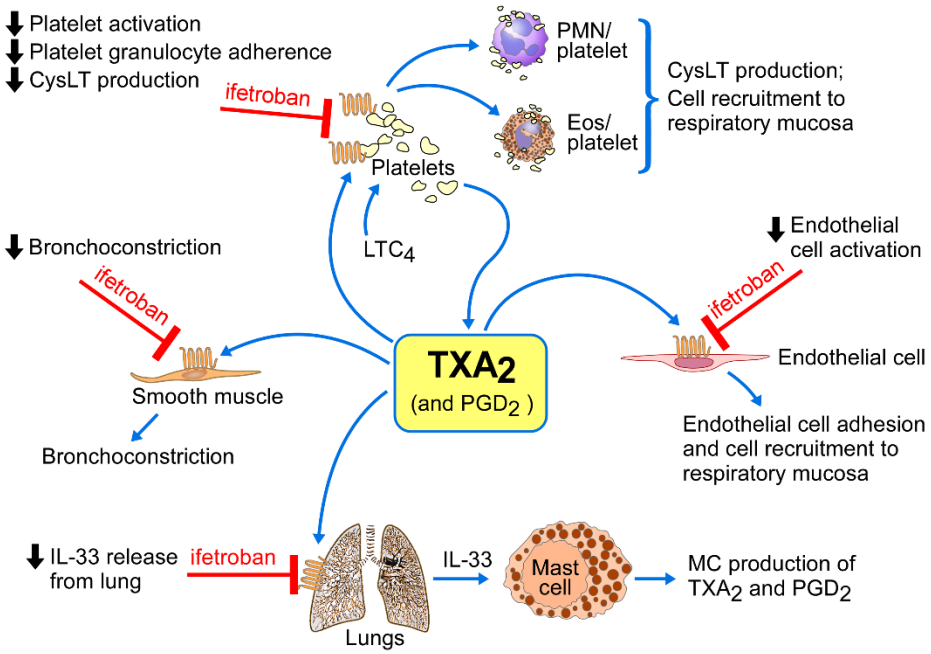
Ifetroban is a new chemical entity under development by Cumberland Pharmaceuticals Inc. (CPI) for aspirin exacerbated respiratory disease (AERD) and other diseases. The current formulation of oral ifetroban is a 50 mg capsule. Ifetroban is a well characterized pharmacological antagonist of the thromboxane prostanoid receptor (TPr), and has been studied previously in healthy volunteers and subjects with cardiovascular diseases. A large safety database exists from this work. CPI is currently studying an intravenous formulation of ifetroban in subjects with hepatorenal syndrome and portal hypertension, and the oral formulation in systemic sclerosis.

AERD affects 7-10% of all asthmatics and ~15% of severe asthmatics (Rajan 2015). AERD is characterized clinically by asthma, severe rhinosinusitis with nasal polyposis, tissue eosinophilia, and characteristic respiratory reactions to ingestion of aspirin and other nonselective inhibitors of cyclooxygenase-1 (COX-1) (White 2012). Biochemically, AERD is marked by over-activity of the 5-lipoxygenase (5-LO) pathway and high levels of leukotriene $E_4$ ($LTE_4$), the stable end-product of cysteinyl leukotriene (cysLT) metabolism (Laidlaw 2012). There is no known cure for AERD, but chronic high-dose aspirin therapy is sometimes effective at controlling inflammation as measured by improvement in smell scores, decrease in nasal polyp formation, decrease in sinus infections/sinus surgery, improvement in asthma outcomes, and decreased need for nasal or systemic corticosteroids (Berges-Gimeno 2003). High-dose aspirin therapy does not however prevent cysLT production (Nasser 1995), although it has been shown to reduce end-organ reactivity to LTE4 (Arm 1989) and nasal mucosal expression of CysLT1R (Sousa 2002). Moreover, 30% of subjects find no benefit from high-dose aspirin treatment (Berges-Gimeno 2003).

Preclinical studies revealed that a murine model of AERD generated by dust mite priming of mice lacking PGE2 synthase (Ptges-/- mice) display bronchoconstriction, intrapulmonary platelet and mast cell activation, and release prostaglandin D2 (PGD2) and cysLTs from their lungs in response to aspirin challenge (Liu 2013). These processes are dramatically attenuated by short-term blockade of TPr, or by depletion of platelets. Moreover, longer-term TPr blockade in this model significantly suppresses eosinophilic inflammation by modifying endothelial-driven leukocyte adhesion (Liu 2012) and lung IL-33 expression. Oral administration of ifetroban is capable of both preempting and reversing TPr-induced bronchospasm in rat and guinea pig studies (Schumacher

1990a; Schumacher 1990b). These studies suggest that TPr signaling is essential both upstream and downstream of the cysLTs, and is involved at multiple steps in AERD pathophysiology. TPr, its ligands and cysLTs are critical to a feed-forward network of mediators and cells that perpetuate respiratory inflammation, tissue remodeling, end-organ dysfunction, and clinical reactions to COX-1 inhibitors that define AERD (Figure 5.1).

**Figure 5.1 Overview of role of TPr and ligands in AERD Pathogenesis**




AERD = Aspirin Exacerbated Respiratory Disease; CysLT = cysteinyl leukotriene 1 receptor; Eos = eosinophil; $LTC_4$ = leukotriene $C_4$; MC = mast cell; $PGD_2$ = prostaglandin $D_2$; PMN = polymorphonuclear leukocytes; TPr = thromboxane prostanoid receptor; $TXA_2$ = thromboxane $A_2$

In a small placebo-controlled safety study designed to investigate ifetroban 200 mg once daily in subjects with a history of AERD prior to and during an aspirin challenge, there were several noteworthy trends in favor of the ifetroban group: greater improvements to PNIFR and TNSS, half of all initial aspirin-provoked reactions occurred at a higher dose of aspirin, and fewer rescue medications were required in response to the aspirin-provoked reaction. The safety results demonstrated ifetroban did not cause a respiratory reaction nor did ifetroban worsen symptoms during the aspirin challenge compared to placebo. There were no treatment-related adverse events reported in the ifetroban group prior to the aspirin challenge. Collectively, these observations in both mice and humans suggest the TPr plays a major role in AERD and that blockade of this pathway may improve baseline disease control in AERD and blunt the feed-forward loop that drives the disease.

## 5.2 Stage of Development

CPI-IFE-006 is a randomized, double-blind, placebo-controlled, Phase 2 study to evaluate oral ifetroban administered daily for eight weeks in subjects with symptomatic AERD.

Approximately 76 subjects will be randomized into two treatment groups of 38 subjects per group.

## 5.3 Trial Rationale

The proposed trial of ifetroban is based on preliminary data from both preclinical models and clinical studies supporting the role of TPr as a central mediator and potential therapeutic target in AERD. Preclinically, ifetroban blocks all features of the reactions to aspirin in AERD-like Ptges-/- mice including preventing cysLT and PGD2 generation. PGD2, along with the classical TPr agonist, thromboxane A2 (TXA2), may be acting in concert to cause bronchoconstriction and sino-nasal symptoms in AERD subjects. Clinical studies identified subjects with AERD as having elevated levels of TPr-active metabolites in their urine (Bochenek 2003) and these levels increase further during an aspirin challenge and correlate with both a decrease in FEV1 and TNSS (Cahill 2015). Further, expression of both thromboxane A2 synthase (TBXAS) and TPr are markedly elevated in nasal polyps from subjects with AERD thus potentially driving the effects of TXA2 and TPr within the feed-forward loop (unpublished).

Ifetroban is under development as a potential novel treatment for AERD. CPI-IFE-006 is a proof-of-concept Phase 2 study designed to investigate the effect of eight weeks of 200 mg daily, oral ifetroban-mediated TPr inhibition in symptomatic AERD subjects.

## 5.4 Dose Rationale

Oral ifetroban doses ≥ 100 mg have been shown to inhibit TPr induced platelet aggregation, with corresponding plasma $C_{max}$ levels of > 500 ng/mL. The bioavailability of oral ifetroban capsules has previously been found to be ≈ 42%. Our recent safety study in subjects with a history of AERD found oral ifetroban at 200 mg daily to be safe and well tolerated. There were no respiratory reactions or symptoms caused by ifetroban alone and no worsening of symptoms seen in the ifetroban group compared to the placebo group during the aspirin challenge. These data, taken together with the safety data of doses up to 500 mg, support a 200 mg oral ifetroban dose for use in this study. A placebo treatment arm will be included in this study to help provide data on the spontaneous response rate in symptomatic AERD.

## 5.5 Risk-Benefit Assessment

Ifetroban prevents TPr ligand binding and activation which plays a key role in the pathophysiology of AERD. Phase 2a data in AERD demonstrated a signal of efficacy for ifetroban compared to placebo with improvements seen in PNIFR and TNSS both before and during the aspirin challenge, higher provoking doses of aspirin and fewer rescue medications. While the aim of the Phase 2a study was safety, these encouraging trends provide a compelling case to further evaluate whether ifetroban will provide a benefit to subjects with AERD. This subsequent Phase 2 study aims to explore this signal in symptomatic AERD subjects in the absence of an aspirin challenge. The anticipated risks associated with the administration of oral ifetroban are well understood given the mechanism of action and its current safety database comprised of over 1,300 subjects. Based upon the current available data for ifetroban and the review of the data by an independent data monitoring committee, no important identified risks have been established. There is a potential risk based on the mechanism of action that treatment with a TPr antagonist may inhibit platelet function and thereby increase the risk of bleeding in AERD subjects. Although our Phase 2a study in subjects with a history of AERD did not demonstrate any abnormal laboratory findings or bleeding events, clinical laboratory results will be monitored for possible abnormalities related to clotting or bleeding in all study subjects.

Given the preclinical and clinical data, there is a potential benefit to study subjects randomized to the ifetroban arm to experience a reduction in the incidence and severity of respiratory reactions. If TPr antagonism does indeed provide symptom control and improve the quality of life (QoL) for subjects with AERD, it would support the use of ifetroban as a therapeutic agent. As such, the potential risk to subjects seems reasonable compared to the potential benefit.

# 6 STUDY OBJECTIVES & ENDPOINTS

## 6.1 Primary Objective

To determine the therapeutic efficacy of ifetroban to improve sino-nasal symptoms and QoL in the treatment of AERD.

## 6.2 Secondary Objectives

To evaluate ifetroban in symptomatic AERD subjects with regards to: pulmonary function, subject-reported outcomes and QoL scales, pharmacodynamics responses based on TPr blockade, frequency and severity of exacerbations, sinus infections and the use of rescue medications and antibiotics.

## 6.3 Primary Efficacy Endpoint

The primary endpoint of the study is the Change From Baseline (CFB) at Week 8 in SNOT-22 score (see Section 16.4). The primary analysis will compare this outcome for each study subject after treatment with ifetroban compared to placebo. The SNOT-22 is a validated questionnaire to assess the impact of chronic rhinosinusitis (CRS) on QoL. This 22-item outcome measure on a 5-category scale is applicable to sino-nasal conditions and surgical treatments. The score ranges from 0 to 110. Higher total scores on the SNOT-22 imply a greater impact of CRS on QoL. The questionnaire was found easy to use with a time to completion of seven minutes and provided good discriminant validity (Hopkins 2009). The SNOT-22 was validated and recommended for routine clinical practice. The Minimal Clinically Important Difference (MCID) is ≥ 8.90.

## 6.4 Secondary Efficacy Endpoints and Other Exploratory Endpoints

### 6.4.1 Second and Exploratory Efficacy Endpoints

- Subject reported symptoms:
  - Asthma Control Questionnaire (ACQ-7)
  - Total Nasal Symptom Score (TNSS)
- FEV1 and peak Nasal Inspiratory Flow Rate (PNIFR)
- University of Pennsylvania Smell Identification test (UPSIT)
- Frequency and severity of asthma exacerbations and chronic sinusitis
- Use of rescue medication and antibiotic use
- Urinary leukotriene E4 and PG metabolite levels
- Serum leukotriene B4 levels
- Blood eosinophil count
- Fractional exhaled Nitric oxide (FeNO)
- Nasal epithelial, urinary and plasma eicosanoid levels

### 6.4.2 Safety Endpoints

The same safety endpoints will be applied across all study subjects. These include adverse events, vital signs, physical exams and clinical laboratory tests.

# 7 STUDY DESCRIPTION

## 7.1 Study Design

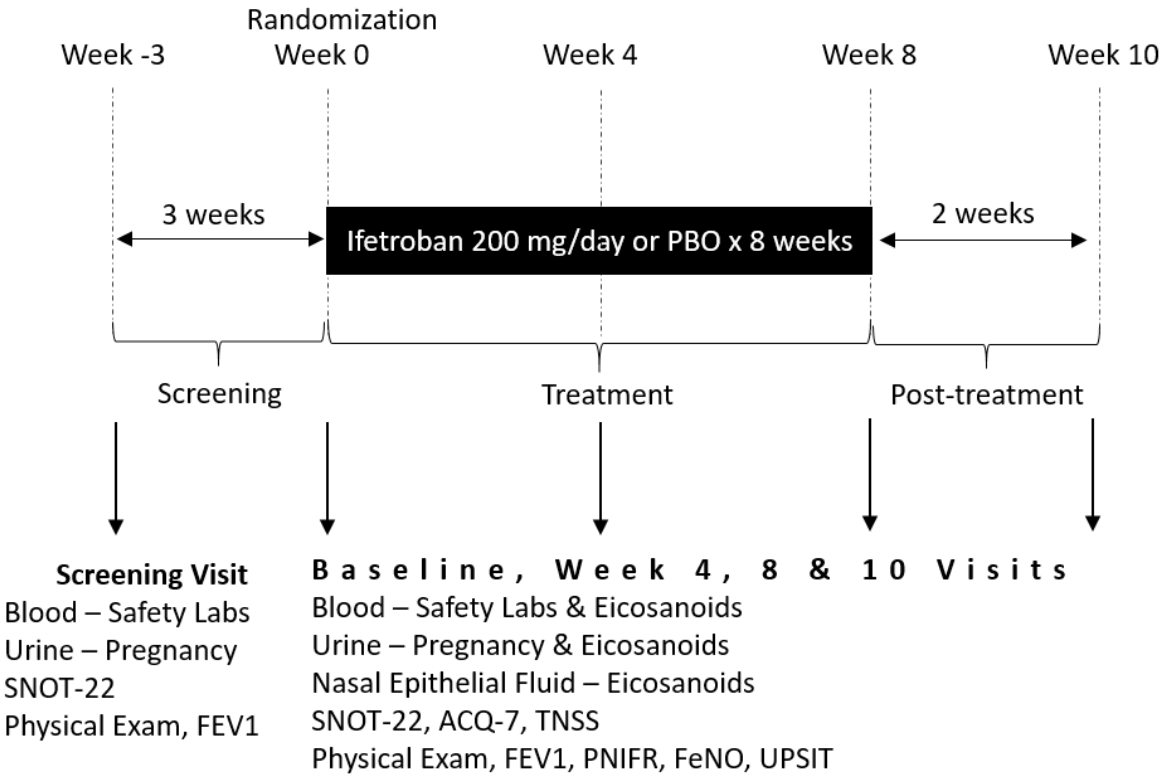
CPI-IFE-006 is a randomized, double-blind, placebo-controlled Phase 2 study to evaluate oral ifetroban administered daily for eight weeks in symptomatic AERD subjects.

Approximately 76 subjects will be randomized into two treatment groups of 38 subjects per group.

The clinical study will be conducted with 3 periods:

- Screening period of up to three weeks
- Randomized ifetroban/placebo treatment period of eight weeks
- Post-treatment period for safety and efficacy of two weeks

**Figure 7-1 Study Design**




ACQ = Asthma Control Questionnaire; FeNO = Fractional exhaled nitric oxide; FEV1 = forced expiratory volume in one second; PBO = placebo; PD = pharmacodynamic; PNIFR = peak Nasal Inspiratory Flow Rate; SNOT = Sino-nasal Outcome Test; TNSS = Total Nasal Symptom Score; UPSIT = Smell Identification Test

The total duration of the study participation for each subject is up to 13 weeks. Recruitment is planned to stop when approximately 76 subjects are randomized. The end of the study is defined as the last subject's last visit/contact.

## 7.2 Randomization and Blinding Conditions and Methods

Subjects who meet all the inclusion and no exclusion criteria during the Screening/Baseline Period will be randomized using a 1:1 randomization ratio to receive either ifetroban 200 mg daily or placebo. A central randomization will be utilized. Approximately 76 subjects shall be randomized to ensure at least 38 subjects per group will be analyzed for efficacy.

The study will be double blind with respect to the treatment assignment. To maintain the study blind, the appearance of packaging and capsules will be identical in both study arms. Site and CPI clinical staff will be blinded to the treatment assignment until the completion of the study. Individual treatment assignment will remain blinded throughout the study. In the event a treatment assignment needs to be unblinded for safety reasons, the site principal investigator will notify the study project manager, who will consult with the medical monitor. The medical monitor will review the circumstances and grant approval as indicated. Any intentional or unintentional breaking of the blind should be reported to the Sponsor immediately and fully documented in the subject's case report form.

## 7.3 Drugs and Dosages

Oral ifetroban is available as the sodium salt of the free acid and is for investigational use only. The drug is supplied as a capsule dosage form (size # 1, white opaque) for oral administration. 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. Capsules are only available at one strength of the sodium salt, i.e., 52.5 mg corresponding to a free-acid dose of 50 mg.

Matching placebo 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.

The bottles of oral Ifetroban or placebo will contain the following information on the label:

**PLACEBO OR IFETROBAN CAPSULES 50MG**
Quantity: 75 Capsules
Instruction: Take capsules by mouth as directed.
Store at controlled room temperature, 20ºC – 25ºC (68ºF – 77ºF)
Caution: New Drug-Limited by Federal law to investigational use
Cumberland Pharmaceuticals Inc.

Additionally, each individual bottle will be labelled with a unique numeric code that identifies the contents to the unblinded sponsor representative. Four (4) capsules each of IMP (oral ifetroban or matching placebo) will be taken by mouth per daily dose during the Treatment Period.

## 7.4 Selection of Study Population

Study eligibility will be determined by the Investigator based on the inclusion and exclusion criteria below.

### 7.4.1 Inclusion Criteria

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

1. History of physician-diagnosed asthma
2. History of nasal polyposis
3. History of at least **two** reactions to oral aspirin or other nonselective cyclooxygenase inhibitor with features of lower airway involvement (cough, chest tightness, wheezing, dyspnea) or one reaction that was life-threatening and required hospitalization, **or** diagnosis of AERD via a physician-conducted challenge to aspirin in the last five years before starting treatment
4. Stable asthma (post-bronchodilator FEV1 of ≥ 60%, no glucocorticoid burst for at least two weeks prior to starting treatment, no hospitalizations or emergency room visits for asthma at least three months prior to starting treatment and not on a dose >1000 µg fluticasone or equivalent daily).
5. ≥ 18 years of age
6. Exhibit symptomatic AERD within three weeks of starting treatment by demonstrating a score of at least 20 on the SNOT - 22

### 7.4.2 Exclusion Criteria

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

1. Current smoking, defined as daily tobacco smoking in the last six months and at least one instance of tobacco smoking in the last three months
2. Current pregnancy or breastfeeding
3. Use of oral or systemic steroids (e.g. prednisone or equivalent) > 20 mg daily in the last four weeks before starting treatment
4. Daily use of long-acting antihistamines in the last two weeks before starting treatment
5. Less than 12 months of allergy shots (maintenance dose of allergy shots are allowed if treatment duration exceeds 12 months). Less than 1 month of 5-lipoxygenase inhibitors (e.g. zileuton) and/or leukotriene receptor antagonists (e.g. montelukast).
6. Any use of nonsteroidal anti-inflammatory drugs (NSAIDs) or any drug that inhibits the cyclooxygenase enzyme in the last two weeks before starting treatment
7. History of bleeding diathesis or use of anticoagulant or antiplatelet drugs in the last 2 weeks before starting treatment
8. Any immunosuppressive treatment including but not limited to methotrexate, cyclosporine, mycophenolate, tacrolimus, gold, penicillamine, sulfasalazine, hydroxychloroquine, azathioprine and cyclophosphamide in the last two weeks before starting treatment (maintenance dose of allergy shots are allowed if treatment duration exceeds 12 months). Biologics/immunotherapies such as Xolair or Nucala are permitted if duration exceeds three months.
9. Endoscopic sinus surgery / polypectomy within the past three months
10. Previously treated in any clinical trial with ifetroban
11. Previously treated with other investigational drugs within eight weeks or five half-lives, whichever is longer, before screening
12. Conditions/concomitant disease which make the participant unevaluable for the efficacy endpoints

## 7.5 Concomitant Medications

A concomitant medication is any treatment received by the subject concomitantly to the IMP. **All concomitant medication use will be tracked in the subject diary and recorded in the**

**appropriate Case Report Form (CRF).** All subjects must be protected by one of the following acceptable forms of effective contraception during the study:

- Established use of oral, injected or implanted hormonal contraceptive

- "Double barrier" methods (i.e., Double Intrauterine device with copper or intrauterine system with progestogen and barrier contraceptive [condom, diaphragm or cervical/vault caps] used with spermicide [foam, gel, film, cream or suppository])

- Female sterilization (e.g., tubal occlusion, hysterectomy or bilateral salpingectomy)

- Male sterilization with post-vasectomy documentation of the absence of sperm in the ejaculate; for female subjects enrolled in the study, the vasectomized male partner should be the sole partner for that subject

The following concomitant medications are allowed.

a. Inhaled, oral or nasal corticosteroids: subjects on a stable dose ≥ 30 day prior to starting IMP. Use of oral or systemic steroids (e.g. prednisone or equivalent) must be at a stable dose ≤ 20 mg daily. Modifications are allowed if symptoms require a change in dose or frequency. All use must be tracked in the subject diary and recorded in the appropriate CRF.

b. Inhaled long-acting beta-adrenergic agonists and anti-muscarinic receptor antagonists: subjects may enter the trial on such medications based on the underlying condition. Modifications are allowed if symptoms require a change in dose or frequency. All use must be tracked in the subject diary and recorded in the appropriate CRF.

c. Inhaled short-acting beta-adrenergic agonists (PRN use): subjects may enter the trial on such medications based on the underlying condition. All use must be tracked in the subject diary and recorded in the appropriate CRF.

d. Nasal budesonide rinses

e. Short-term use of antibiotics (< 2 weeks)

f. Daily use of long-acting antihistamines are prohibited two weeks before starting treatment however subjects may administer such medications on an **as-needed basis only** based on the underlying condition. All use must be tracked in the subject diary and recorded in the appropriate CRF.

g. Maintenance dose of allergy shots if treatment duration exceeds 12 months

h. Use of 5-lipoxygenase inhibitors (e.g. zileuton) and leukotriene receptor antagonists (e.g. montelukast) if subjects are on a stable dose for ≥ 30 days.

i. Use of biologics/immunotherapies such as Xolair or Nucala if subjects are on a stable dose for ≥ three months.

## 7.6 Prohibited Medications or Procedures

Before randomization, a medication history will be collected for each subject to ensure that no prohibited medications and procedures will be taken during the study. The following medications and procedures are prohibited during the screening, treatment and post-treatment periods:

- Use of oral or systemic steroids (e.g. prednisone or equivalent) > 20 mg daily in the last four weeks before starting treatment

- Daily use of long-acting antihistaminesin the last two weeks before starting treatment. Please note: **daily use of long-acting antihistamines is prohibited** however subjects may administer such medications on an **as-needed basis only** based on the underlying condition. All use must be tracked in the subject diary and recorded in the appropriate CRF.

- Any use of nonsteroidal anti-inflammatory drugs (NSAIDs) or any drug that inhibits the cyclooxygenase enzyme in the last two weeks before starting treatment

- Use of warfarin or any other antiplatelet or anticoagulant medications in the last two weeks before starting treatment

- Long-term use of systemic antibiotics (> 2 weeks)

- Any immunosuppressive treatment including but not limited to methotrexate, cyclosporine, mycophenolate, tacrolimus, gold, penicillamine, sulfasalazine, hydroxychloroquine, azathioprine and cyclophosphamide (maintenance dose of allergy shots are allowed if treatment duration exceeds 12 months). Biologics/immunotherapies such as Xolair or Nucala are permitted if duration exceeds three months.

- Endoscopic sinus surgery / polypectomy within the past three months prior to starting treatment

## 7.7 Dietary Requirements

Multiple food effect studies have demonstrated that high fat, protein or carbohydrate meals all had a similar effect of decreasing the maximum serum concentration ($C_{max}$) (average of 80-90%),

prolonging the time of maximum plasma concentration ($T_{max}$) (8-12 fold), and decreasing the area under the concentration time-curves from time zero to infinity ($AUC_{0-\infty}$) of ifetroban (average of 25-35%) compared to the fasting state.

For this reason, ifetroban and placebo should be taken at least 30 minutes before a meal or six hours after a meal.

# 8 STUDY VISITS AND PROCEDURES

## 8.1 Overview – Schedule of Time and Events

This 13-Week study will consist of a three-week Screening Period (Week -3 to Week 0), an 8-week Treatment Period (Week 0 to Week 8) and a two-week Post-treatment Period (Week 8 to Week 10). The study visits occur on the planned dates relative to the first dose of IMP as scheduled. The visit schedule should be adhered to within the ± 5 day visit window.

If a subject is prematurely discontinued from treatment, all assessments planned at the End of Treatment visit should be performed. Prior to all screening assessments, after discussion of participation in the study, the written consent form must be signed and dated. Although the screening assessments for this study are grouped under the heading of a single visit in this protocol, it is possible for them to be performed over more than one site visit if necessary, as long as the three-week screening period relative to the first dose of IMP is respected. Subjects that fail screening for exclusion criteria, for example concomitant medications, acute illness (upper respiratory tract infection), required drug-specific discontinuation periods or laboratory tests, may be rescreened for study eligibility one additional time.

### 8.1.1 Screening Period

The Screening Period is defined as the three-week period prior to Week 0 (IMP administration).

Before the initiation of study-specific screening assessments, the subject must be given a complete explanation of the purpose of the study and evaluations that will be made as part of the study. Subsequently, the subject must sign and receive a copy of an Informed Consent Form that was approved by the Institutional Review Board **(**IRB)/Independent Ethics Committee (IEC). Once informed consent has been obtained, the eligibility of the subject to participate in this study will be determined by the Investigator on the basis of the inclusion and exclusion criteria in Section 7.4. Screening Period assessments will also be performed to determine eligibility. Only eligible subjects will be randomized to receive IMP at Week 0.

Following a discussion of participation in the clinical study and signed informed consent obtained, the following procedures will be performed to determine the subject's eligibility for this study (Table 8–1) during the Screening Period (Week -3 to Week 0):

- Informed Consent
- Interview to collect subject medical history, including but not limited to, disease history (including asthma history, number of asthma exacerbations in the previous year, hypersensitivity to aspirin or other NSAIDs), surgical history (including the number and dates of previous nasal polypectomies), recently discontinued and concomitant medications (include all background therapy for AERD).
- Demographic data
- Administer SNOT-22.
- Perform spirometry to ensure the subject has stable asthma (FEV1 ≥ 60% of predicted normal and has not experienced any exacerbation requiring treatment with ≥ 1 systemic (oral or parenteral) steroid bursts for worsening asthma and/or hospitalization or an emergency/urgent medical care visit for worsening asthma in the previous three months or are on a dose of inhaled corticosteroids > 1000 µg fluticasone or equivalent daily).
- Obtain fasting blood samples for screening clinical laboratory determinations:
    - Hematology: To include hemoglobin, hematocrit, platelet count, total white blood cell count with five-part differential count, and total red blood cell count.
    - Serum chemistry: To include creatinine, blood urea nitrogen, glucose, uric acid, total cholesterol, total protein, albumin, total bilirubin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, electrolytes (sodium, potassium, chloride), bicarbonate, and creatine phosphokinase.
    - Prothrombin time (PT) and international normalized ratio (INR)
- Review entry criteria to assess eligibility with special attention to verify the following:
    - History of at least **two** reactions to oral aspirin or other nonselective cyclooxygenase inhibitor with features of lower airway involvement (cough, chest tightness, wheezing, dyspnea) or one reaction that was life-threatening and required

hospitalization, **or** diagnosis of AERD via a physician-conducted challenge to aspirin in the last five years before starting treatment

- Use of oral or systemic steroids (e.g. prednisone or equivalent) > 20 mg daily in the last four weeks before starting treatment, daily use of long-acting antihistamines in the last two weeks before starting treatment. Subjects on 5-lipoxygenase inhibitors (e.g. zileuton) and/or leukotriene receptor antagonists (e.g. montelukast) must be on a stable dose for ≥ 30 days before starting treatment. No NSAID, anticoagulants and immunosuppressive medication use is allowed.

- Presence of a score of at least 20 on the SNOT - 22

- Perform physical examination including vital signs [blood pressure, heart rate, respiration rate, body temperature, weight (kg), height (cm)]

- Obtain pregnancy test if female of child-bearing potential (pre-menopausal female biologically capable of becoming pregnant). Confirm subject is protected by one of the following acceptable forms of effective contraception during the study:

  - Established use of oral, injected or implanted hormonal contraceptive

  - "Double barrier" methods (i.e., Double Intrauterine device with copper or intrauterine system with progestogen and barrier contraceptive [condom, diaphragm or cervical/vault caps] used with spermicide [foam, gel, film, cream or suppository])

  - Female sterilization (e.g., tubal occlusion, hysterectomy or bilateral salpingectomy)

  - Male sterilization with post-vasectomy documentation of the absence of sperm in the ejaculate; for female subjects enrolled in the study, the vasectomized male partner should be the sole partner for that subject

- Dispense subject diary, provide instructions for daily use and remind subject to bring it to the next visit.

- Schedule appointment for next visit

### 8.1.2 Treatment Period

**Week 0 Start of Treatment Visit – Randomization**

After the three-week Screening Period, subjects will come into the site for Week 0 Visit.

- Interval history, record baseline signs and symptoms, record all medication use with start date and dose and check for prohibited medications.

- Perform a limited physical exam with vital signs (blood pressure, heart rate, respiration rate, body temperature, weight)
- Administer TNSS, ACQ-7, and SNOT-22
- Obtain spirometry result and record in the electronic CRF (eCRF)
- Reconfirm eligibility based on review of Inclusion/Exclusion criteria

A subject will be considered to have failed screening if entry criteria are not met and should be discontinued.

**If the subject meets all inclusion and does not meet any exclusion criteria:**

- Subject will be randomized
- PNIFR and FeNO will be recorded
- Perform serum/urine pregnancy test (for women of childbearing potential). Confirm subject is protected by one of the following acceptable forms of effective contraception during the study:

  - Established use of oral, injected or implanted hormonal contraceptive

  - "Double barrier" methods (i.e., Double Intrauterine device with copper or intrauterine system with progestogen and barrier contraceptive [condom, diaphragm or cervical/vault caps] used with spermicide [foam, gel, film, cream or suppository])

  - Female sterilization (e.g., tubal occlusion, hysterectomy or bilateral salpingectomy)

  - Male sterilization with post-vasectomy documentation of the absence of sperm in the ejaculate; for female subjects enrolled in the study, the vasectomized male partner should be the sole partner for that subject

- Perform blood sampling (prior to administration of IMP) for clinical laboratories: hematology, chemistry, PT, and INR.

Note: Clinical laboratory testing at Week 0 Visit is limited to biomarkers in serum and plasma if screening labs were performed within three weeks of starting IMP treatment.

- Collect urine and blood samples for eicosanoid metabolites.
- Collect nasoabsorptive matrix for eicosanoid measurements.

- Conduct a smell test (UPSIT)
- Collect data from subject diary and remind subject to record daily medication usage including IMP, exacerbations, rescue medication or antibiotic usage, if applicable, twice daily TNSS (AM and PM) and to bring their diary to the next visit
- Pre-IMP Dietary Assessment
- Dispense IMP and administer IMP
- Commence AE reporting
- Schedule appointment for next visit

Treatment Period (Week 0 to Week 8): Subjects will take ifetroban or placebo daily for eight weeks. There will be a telephone encounter one week into this Treatment Period to ensure safety and confirm that baseline asthma symptoms have not worsened.

**Week 4 Treatment Visit**

After four weeks of treatment, subjects will return to the site for Week 4 Treatment Visit.

- Record all medication use with start date and dose and check for prohibited medications.
- Inquire about AEs/Serious Adverse Events (SAEs) and IMP tolerability
- Perform a limited physical exam with vital signs (blood pressure, heart rate, respiration rate, body temperature, weight)
- Administer TNSS, ACQ-7, and SNOT-22
- Obtain spirometry, PNIFR and FeNO
- Perform serum/urine pregnancy test (for women of childbearing potential) Confirm subject is protected by one of the following acceptable forms of effective contraception during the study:

  - Established use of oral, injected or implanted hormonal contraceptive

  - "Double barrier" methods (i.e., Double Intrauterine device with copper or intrauterine system with progestogen and barrier contraceptive [condom, diaphragm or cervical/vault caps] used with spermicide [foam, gel, film, cream or suppository])

- Female sterilization (e.g., tubal occlusion, hysterectomy or bilateral salpingectomy)

- Male sterilization with post-vasectomy documentation of the absence of sperm in the ejaculate; for female subjects enrolled in the study, the vasectomized male partner should be the sole partner for that subject

- Collect urine and blood samples for eicosanoid metabolites.
- Collect nasoabsorptive matrix for eicosanoid measurements.
- Conduct a smell test (UPSIT)
- Review subject diary for IMP compliance, content and completeness; collect data from subject diary and remind subject to continue recording daily medication usage including IMP, time of meals and doses, exacerbations, rescue medication or antibiotic usage (if applicable), twice daily TNSS (AM and PM) and to bring their diary to the next visit
- Dispense IMP and administer IMP
- Schedule appointment for next visit

**Week 8 End of Treatment Visit**

After four additional weeks of treatment, subjects will return to the site for Week 8 End of Treatment Visit.

- Record all medication use with start date and dose and check for prohibited medications.
- Inquire about AEs/SAEs and IMP tolerability
- Perform a limited physical exam with vital signs (blood pressure, heart rate, respiration rate, body temperature, weight)
- Administer TNSS, ACQ-7, and SNOT-22
- Obtain spirometry, PNIFR and FeNO
- Perform serum/urine pregnancy test (for women of childbearing potential). Confirm subject is protected by one of the following acceptable forms of effective contraception during the study:

  - Established use of oral, injected or implanted hormonal contraceptive

- "Double barrier" methods (i.e., Double Intrauterine device with copper or intrauterine system with progestogen and barrier contraceptive [condom, diaphragm or cervical/vault caps] used with spermicide [foam, gel, film, cream or suppository])

- Female sterilization (e.g., tubal occlusion, hysterectomy or bilateral salpingectomy)

- Male sterilization with post-vasectomy documentation of the absence of sperm in the ejaculate; for female subjects enrolled in the study, the vasectomized male partner should be the sole partner for that subject

- Perform blood sampling for clinical laboratories: hematology, chemistry, PT, and INR.
- Collect urine and blood samples for eicosanoid metabolites.
- Collect nasoabsorptive matrix for eicosanoid measurements.
- Conduct a smell test (UPSIT)
- Review subject diary for IMP compliance, content and completeness; collect data from subject diary and remind subject to continue recording daily medication usage, time of meals and doses, exacerbations, rescue medication or antibiotic usage (if applicable), twice daily TNSS (AM and PM) and to bring their diary to the next visit
- Schedule appointment for next visit

### 8.1.3 Post-treatment Period

After two weeks post-treatment, subjects will return to the site for Week 10 Post-treatment Visit.

- Record all medication use with start date and dose and check for prohibited medications.
- Inquire about AEs/SAEs
- Perform a limited physical exam with vital signs (blood pressure, heart rate, respiration rate, body temperature, weight)
- Administer TNSS, ACQ-7, and SNOT-22
- Obtain spirometry, PNIFR and FeNO
- Perform blood sampling for clinical laboratories if abnormal at Week 8 only: hematology, chemistry, PT, and INR.

- Collect urine and blood samples for eicosanoid metabolites.
- Collect nasoabsorptive matrix for eicosanoid measurements.
- Conduct a smell test (UPSIT)
- Review subject diary for content and completeness; collect data from subject diary
- Propose the optional qualitative self-assessment of the treatment to the subject

## Table 8–1 Schedule of Treatment & Events

| | Screening Period | Treatment Period | | | | Post-treatment Period |
|---|---|---|---|---|---|---|
| | Visit(s) | Visit | Phone Call | Visit | Visit | Visit |
| | Week -3 to Week 0 | Week 0 | Week 1 | Week 4 (± 5 days) | Week 8 (± 5 days) | Week 10 (± 5 days) |
| **Informed Consent** | X | | | | | |
| **Inclusion/Exclusion Criteria** | X | | | | | |
| **Medical & Surgical History** | X | | | | | |
| **Subject Demography** | X | | | | | |
| **Physical Exam with vital signs** | X | | | | | |
| **Limited Physical Exam with vital signs** | | X | | X | X | X |
| **Spirometry (FEV1)** | X | X | | X | X | X |
| **PNIFR and FeNO** | | X | | X | X | X |
| **Pregnancy Test (Serum/Urine)[a]** | X | X | | X | X | X |
| **Hematology[b]** | X | X[d] | | | X | X[e] |
| **PT, INR, Chemistry[c]** | X | X[d] | | | X | X[e] |
| **SNOT-22, TNSS, ACQ-7** | X[f] | X | | X | X | X |
| **Smell test (UPSIT)** | | X | | X | X | X |
| **Collect urine & blood for eicosanoid levels** | | X | | X | X | X |
| **Collect nasoabsorptive matrix for eicosanoid levels** | | X | | X | X | X |
| **Self-assessment of the treatment (optional)** | | | | | X | |
| **Dispense IMP** | | X | | X | | |
| **IMP Dosing** | | **I----------Continual Once Daily Dosing (200 mg/day)---------I** | | | | |
| **Record Concomitant Medications** | **I----------Continual----------I** | | | | | |
| **AE/SAE Recording (if any)** | | **I----------Continual----------I** | | | | |
| **Dispense, review and/or collect subject diary** | | X | | X | X | X |

a) For women of childbearing potential; b) Hemoglobin, hematocrit, platelet count, total white blood cell count with five-part differential count, and total red blood cell count; c) Creatinine, blood urea nitrogen, glucose, uric acid, total cholesterol, total protein, albumin, total bilirubin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, electrolytes (sodium, potassium, chloride), bicarbonate, and creatine phosphokinase; d) Week 0 hematology, chemistry, PT and INR do not have to be repeated if Screening labs were performed within 3 weeks of starting IMP; e) Week 10 hematology, chemistry, PT and INR only performed for abnormal labs at Week 8; f) SNOT-22 only at Screening; All 3 questionnaires are required at subsequent visits.

ACQ-7 = Asthma Control Questionnaire; AE = adverse event; FEV1 = Forced Expiratory Volume in 1 Second; FeNO = Fractional exhaled Nitric oxide; IMP = Investigational Medicinal Product; INR = international normalized ratio; PNIFR = Peak Nasal Inspiratory Flow Rate; PT = prothrombin time; SAE = serious adverse event; SNOT = Sino-nasal Outcome Test; TNSS = Total Nasal Symptom Score; UPSIT = Smell Identification Test

# 9 SUBJECT DISCONTINUATION AND STUDY OR SITE TERMINATION

## 9.1 Subject Discontinuation

Subjects will be encouraged to complete the study; however, they may voluntarily withdraw at any time. The Investigator will provide a report in the CRF describing the reason for discontinuation. If a subject withdraws before completion, every effort should be made to complete the assessments scheduled during the final scheduled assessment.

A subject may be terminated early from the study for the following reasons:

- The subject elects to withdraw consent from all future study activities, including follow-up.
- The subject is "lost to follow-up" (i.e., no further follow-up is possible because attempts to reestablish contact with the participant have failed).
- The subject dies.
- The subject develops a medical condition or is started on new medication(s) prohibited by the study or not previously mentioned in the list of prohibited medications that, in the opinion of the investigator, may pose additional risks from participation in the study, may interfere with the subject's ability to comply with study requirements or that may impact the quality of the data obtained from the study.
- If, in the course of an asthma exacerbation, a study investigator decides to discontinue study medication (ifetroban/placebo), the subject will be withdrawn from the study.
- In addition, subjects must be withdrawn from the study if any of the following occur:
    - Any serious adverse event related to study medication (ifetroban/placebo or aspirin) or to a study procedure
    - Serious arrhythmia requiring therapy
    - Thrombocytopenia $< 50 \times 10^9$/L
    - Anemia (a fall in baseline hemoglobin of 10% or more)
    - Gastrointestinal bleeding

- Pregnancy

Subjects who are prematurely terminated from the study will be followed to monitor safety for a minimum of 30 days or until resolution of the disqualifying event, whichever is longer, or until the Independent Safety Monitor, the CPI Director of Medical Affairs and the Principal Investigator determine that the follow-up is complete.

Subjects with early termination from this study will not be replaced.

## 9.2 Study or Site Termination

If the Sponsor, Investigator, Independent Safety Monitor, Study Monitor, or appropriate regulatory officials discover conditions arising during the study that indicate that the study should be halted or that the study center should be terminated, this action may be taken after appropriate consultation among the Sponsor, Investigator, Independent Safety Monitor, and Study Monitor.

Conditions that may warrant termination of the study include, but are not limited to, the following:

- The discovery of an unexpected, serious, or unacceptable risk to the subjects enrolled in the study
- A decision on the part of the Sponsor to suspend or discontinue testing, evaluation, or development of the product
- A study conducted at a single study site or a single study site in a multicenter study may also warrant termination under the following conditions:
    - Failure of the Investigator to enroll subjects into the study at an acceptable rate
    - Failure of the Investigator to comply with pertinent regulations of appropriate regulatory authorities
    - Submission of knowingly false information from the research facility to the Sponsor, Study Monitor, or appropriate regulatory authority
    - Insufficient adherence to protocol requirements

Study termination and follow-up will be performed in compliance with the conditions set forth in the International Conference on Harmonization (ICH) sixth efficacy publication (E6) on Good Clinical Practice, section 4.12, ICH E6 4.13, ICH E6 5.20, and ICH E6 5.21.

# 10 ADVERSE EVENTS

Adverse events will be captured in the CRF for this study.

## 10.1 Definitions

### 10.1.1 Adverse Event Definitions

Adverse events are defined according to ICH Harmonized Tripartite Guideline E2A and 21 CFR 312.32.

Adverse event (AE) – is any untoward medical occurrence in a subject or clinical trial subject administered a trial product and which does not necessarily have a causal relationship with this treatment.

An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The following is not considered or documented as an AE in study records:

- Pre-planned procedure (documented as concomitant illness on the CRF at screening) unless the condition for which the procedure was planned has worsened from the first trial-related activity after the subject has signed the informed consent form.

- Pre-existing conditions found as a result of screening procedures unless the condition worsens during treatment.

- Events which are pre-defined as part of the efficacy analysis. However, if events are serious as defined below, events must be reported as such.

Serious adverse event (SAE) – is any untoward medical occurrence or effect that at any dose: results in death; is life-threatening (this refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it was more severe); requires in-subject hospitalization or prolongation of existing hospitalization; results in persistent or significant disability or incapacity; is a congenital anomaly or birth defect; is judged medically important (this refers to an event that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed).

## 10.1.2 Adverse Event Assessment Definitions

**Severity**

The maximum severity of an adverse event is assessed by the investigator using the following definitions:

- Mild: Transient symptoms, no interference with the subject's daily activities.
- Moderate: Marked symptoms, moderate interference with the subject's daily activities.
- Severe: Considerable interference with the subject's daily activities, unacceptable.

**Relationship**

The causal relationship between an adverse event and the trial product is assessed by the investigator using the following definitions:

- Probable: Good reasons and sufficient documentation to assume a causal relationship.
- Possible: A causal relationship is conceivable and cannot be dismissed
- Unlikely: The event is most likely related to an etiology other than the trial product.

An adverse event is considered causally related to the use of the trial product when the relationship assessment is probable or possible. Events assessed as unlikely related to the use of trial product will generally be considered as having no relationship to treatment.

**Outcome**

The outcome of an adverse event is assessed by the investigator using the following definitions:

- Recovered: Fully recovered, or by medical or surgical treatment the condition has returned to the level observed at the first trial-related activity.
- Recovering: The condition is improving and the subject is expected to recover from the event. This term should only be used when the subject has completed the trial.
- Recovered with sequelae: As a result of the AE the subject suffered persistent and significant disability/incapacity (e.g. became blind, deaf, paralyzed). Any AE recovered with sequelae should be classified as SAE.
- Not recovered: The subject's condition has not improved and the symptoms are unchanged

- Fatal

- Unknown: The subject's condition is unknown. This term should only be used when no other definition is possible (e.g. the subject is lost to follow-up).

## 10.2 Collection, Recording and Reporting of Adverse Events

For this study, all events meeting the definition of an adverse event must be collected and reported from the first trial-related activity after the subject signs the informed consent and until end of post-treatment period.

The investigator should record the diagnosis, if available. If no diagnosis is available the investigator should record each sign and symptom as individual adverse events.

The investigator must report initial information on all serious adverse events within 24 hours of obtaining knowledge of the event. Furthermore, the investigator must complete the SAE forms within five days of obtaining knowledge of the SAE. The monitor must be informed accordingly.

The investigator must inform the IRB in accordance with local requirements in force and the ICH guidelines for GCP and the Food and Drug Administration (FDA) Title 21 Code of Federal Regulations, Part 312.32.

## 10.3 Follow-up of Adverse Events

All adverse events classified as non-serious adverse events that are both classified as severe and possibly or probably related to the investigational medicinal product must be followed until the subject has recovered and all queries have been resolved.

For cases of chronic conditions, follow-up until "recovered" is not required. After the subject has completed the trial, these cases can be closed with the outcome "recovering" or "not recovered".

All other non-serious adverse events must be followed until the outcome of the event is "recovering" (for chronic conditions), "recovered" or until the last subject contact/visit/end of post-treatment follow-up period, whichever comes first, and until all queries related to the adverse event have been resolved.

**Follow-up of Serious Adverse Events**

All adverse events classified as serious should be followed until the outcome of the event is "recovered", "recovered with sequelae", or "death" and until all queries have been resolved. For cases of chronic conditions and cancer, follow-up until "recovered", "recovered with sequelae" or

"death" is not required. After the subject has completed the trial, these cases can be closed with the outcome "recovering" or "not recovered".

# 11 STATISTICAL METHODS AND DATA ANALYSIS

The following text provides general description of the statistical methodology for the assessment of efficacy, safety, and tolerability of 200 mg/day of oral ifetroban in this double-blind placebo-controlled study in subjects with symptomatic AERD. Details of the statistical analyses will be provided in the Statistical Analysis Plan, which will be finalized prior to database lock and unblinding. All recorded data will be listed.

## 11.1 Sample Size Determination

Thirty-eight subjects per group will provide 90% power for the comparison of ifetroban and placebo with respect to the change from baseline in SNOT-22 scores at Week 8 (two-sided, level 0.05), assuming a common standard deviation of 16 and a true difference is 12.

## 11.2 Subject Populations for Analysis

### 11.2.1 Safety Population

All subjects who received at least one dose of study medication will be included in the Safety Population.

Treatment emergent period for Safety Population is defined as the time from the first administration of study medication to the end of the post-treatment Period.

### 11.2.2 Intent-to-Treat Population

The Intent-To-Treat (ITT) Population will consist of all treated subjects with at least one post-baseline assessment of SNOT-22.

### 11.2.3 Per Protocol Population

The Per Protocol (PP) Population will consist of all subjects in the ITT population with no major protocol violations, including violation of inclusion or exclusion criteria or insufficient dosing. Inclusion of subjects in the PP Population will be determined prior to unblinding.

## 11.3 Subgroup analysis

To assess the consistency of treatment effects across the subgroup levels, and to examine baseline biomarkers for their potential value to predict treatment response, exploratory subgroup analyses will be conducted for the change from baseline in SNOT-22 with respect to age group, gender,

region, race, baseline SNOT-22, baseline TNSS, baseline ACQ-7 and selected biomarkers prior to the study. The details will be provided in the Statistical Analysis Plan.

## 11.4 Randomization

Subjects will be randomized using a 1:1 randomization ratio for ifetroban 200 mg daily for eight weeks, or placebo daily for eight weeks.

## 11.5 Methods for Handling Missing Data

All missing data will be queried. Missing efficacy data which are not retrievable through queries will be imputed. Binary response variables will be imputed by treating the missing data as a non-response, i.e., non-responder imputation. Missing data for continuous variables will be imputed using Last Observation Carried Forward. Sensitivity analyses may be performed to assess the impact of the imputation technique(s).

## 11.6 Data Analysis Plan

### 11.6.1 Demographic and Baseline Parameters

Demographic and baseline characteristics will be summarized using descriptive statistics or frequency tables, by treatment group and overall.

### 11.6.2 Exposure and Compliance

Exposure and compliance will be summarized for the Safety Population by treatment group and overall. Comments recorded on the Study Drug Accountability CRF page will not be applied in the computation of compliance.

Exposure is the duration (days) of treatment, computed as:

Exposure = Date of Final Dose- Date of Baseline Visit + 1.

Treatment compliance will be calculated as:

Compliance (%) = 100*(Total Number of Capsules Dispensed-Total Number of Capsules Returned)/(4*Exposure).

### 11.6.3 Efficacy Analyses

All hypothesis tests will be performed at the 0.05 level. Analyses of the primary and secondary efficacy variables will be performed using both the ITT and PP Populations. Corresponding summary statistics will be presented for all efficacy analyses.

### 11.6.3.1 Primary Analysis

The primary efficacy endpoint is the CFB in SNOT-22 score and the primary analysis is the analysis of CFB in SNOT-22 at Week 8, using Analysis of Covariance (ANCOVA), with SNOT-22 at Baseline included as the only covariate.

### 11.6.3.2 Analysis of secondary endpoints

CFB in ACQ-7 and CFB in TNSS at Week 8 will be analyzed using ANCOVA, with the corresponding value at Baseline included as the only covariate. These variables, as well as CFB in SNOT-22, at Week 4 will also be analyzed as ancillary analyses.

Analyses of CFB for other continuous efficacy variables will be performed at Weeks 4 and 8 in the same manner using ANCOVA with the corresponding value at Baseline included as the only covariate.

Any improvement in SNOT-22, ACQ-7, and TNSS (Yes or No) at Weeks 4 and 8 will be analyzed using the normal approximation to the binomial distribution, assuming unequal variances.

## 11.6.4 Safety Parameters

All safety data will be summarized. AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) (Version 9.0 or later). All Treatment Emergent Adverse Events (TEAEs) will be summarized by treatment group. Counts and percents will be presented by treatment group for each observed system organ class (SOC) and preferred term as defined in MedDRA.

The preferred terms and SOCs will be summarized in the following set of tables:

- All AEs;
- All AEs by maximum level of intensity;
- All AEs by closest relationship to the study medication.

The frequencies and percentages of AEs will be tabulated. Incidence, relation to study medication, and severity will be summarized.

Physical examination findings, laboratory parameters, vital signs, FEV1, weight, and corresponding changes from Baseline, as appropriate, will be summarized using descriptive statistics at each visit.

# 12 STUDY MANAGEMENT AND DATA COLLECTION

## 12.1 Confidentiality

All information regarding the nature of the proposed investigation provided by the Sponsor or Study Monitor to the Investigator (with the exception of information required by law or regulations to be disclosed to the IRB, the subject, or the appropriate regulatory authority) must be kept in confidence by the Investigator.

The anonymity of participating subjects must be maintained. Subjects will be identified by an assigned subject number on CRFs and other study documents submitted to the Study Monitor. Documents that will not be submitted to the Study Monitor and that identify the subject (e.g., the signed informed consent document) must be maintained in strict confidence by the Investigator, except to the extent necessary to allow auditing by the appropriate regulatory authority, the Study Monitor, or Sponsor representatives.

## 12.2 Source Documents

Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

## 12.3 Case Report Forms

It is the responsibility of the Investigator to maintain adequate and accurate eCRFs designed by the Sponsor to record (according to Sponsor instructions) all observations and other data pertinent to the clinical investigation in a timely manner. All CRFs should be completed in their entirety in a neat, legible manner to ensure accurate interpretation of data.

Should a correction be made, the corrected information will be entered in the e-CRF overwriting the initial information. An audit trail allows for identifying the modification.

Data are available within the system to the Sponsor as soon as they are entered in the e-CRF.

The computerized handling of the data by the Sponsor when available in the eCRF may generate additional requests to which the Investigator is obliged to respond by confirming or modifying the data questioned. The requests with their responses will be managed through the eCRF.

## 12.4 Records Retention

According to CFR21 312.62 (c) and ICH E6 4.9.5, all CRFs, as well as supporting documentation and administrative records, must be retained by the Investigator for a minimum of two years following notification that the appropriate regulatory authority has approved the product for the indication under study, if no application is to be filed or if the application is not approved for such indication, until two years after the investigation is discontinued and FDA is notified. It is the sponsor's responsibility to inform the investigator as to when these documents no longer need to be retained. No study documents will be destroyed or moved to a new location without prior written approval from the Sponsor. If the Investigator relocates, retires, or withdraws from the clinical study for any reason, all records required to be maintained for the study should be transferred to an agreed upon designee, such as the Study Monitor, another Investigator, or the institution where the study was conducted.

# 13 STUDY MONITORING, AUDITING, AND INSPECTING

## 13.1 Study Monitoring Plan

The progress of the study will be monitored by using the following methods:

- Periodic on-site visit(s)
- Telephone communications, as needed, among the Investigator, Clinical Monitor and Medical Monitor
- Review of CRFs and clinical records

# 14 ETHICAL CONSIDERATIONS

This study will be conducted according to the standards of FDA, ICH, GCP Guidelines, IRB regulations, any applicable government regulations and procedures. This protocol and any amendments will be submitted to a properly constituted IRB for approval of the study conduct.

## 14.1 Informed Consent

Written informed consent must be obtained from each subject (or the subject's legal guardian/representative) before performing any Screening Period evaluations. The signed informed consent document will be retained by the Investigator, and a copy will be given to the subject or subject's legal guardian/representative. The informed consent document, which is prepared by the Investigator, must have been reviewed and approved by the Sponsor and the Investigator's IRB before the initiation of the study. The document must contain the 20 elements

of informed consent described in ICH E6 4.8 (Appendix 16.1). Appendix 16.1 provides further details regarding the specific requirements for informed consent. In addition, subjects of appropriate intellectual maturity should provide written informed assent, as determined by the institution's IRB or local legal requirement.

## 14.2 Protocol Compliance

Substantive changes in the protocol include changes that affect the safety of subjects or changes that alter the scope of the investigation, the scientific quality of the study, the experimental design, dosages, assessment variable(s), the number of subjects treated, or the subject selection criteria. Such changes must be prepared as a protocol amendment by the Study Monitor and implemented only upon joint approval of the Sponsor, Investigator, and the Study Monitor. A protocol amendment must receive IRB approval before implementation. In parallel with the IRB approval process, the protocol amendment will be submitted to the appropriate regulatory authority as an amendment to the regulatory submission under which the study is being conducted. If a protocol amendment requires changes in the informed consent document, the revised informed consent document prepared by the Investigator must be approved by the Sponsor, Study Monitor, and the IRB.

Emergency departures from the protocol that eliminate an apparent immediate hazard to a particular subject and that are deemed crucial for the safety and well-being of that subject may be instituted for that subject only. The Investigator or other attending physician also will contact the Medical Monitor as soon as possible in the case of such a departure. These departures do not require pre-approval by the IRB; however, the IRB and Medical Monitor must be notified in writing as soon as possible after the departure has been made. In addition, the Investigator will document in the subject's CRF the reasons for the protocol deviation and the ensuing events.

## 14.3 Study Files

Documentation concerning Investigator data, IRB data, and clinical laboratory data is required before shipment of oral ifetroban to the study site (Appendix 16.2). Copies of these documents as well as supplemental information, such as the Investigator's Brochure and Responsibilities and Obligations of Investigators and Sponsors (Appendix 16.3.2), will be kept on-site in a special study file. This file also will contain drug accountability (receipt/dispensing) records, Sponsor/Investigator correspondence, IRB correspondence, changes to the protocol, information regarding monitoring activities, subject exclusion records, biological samples records, and CRFs. Investigator data, including FDA Form 1572 and statement of qualifications for each Investigator, are provided in Appendix 16.3.2.

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# 16 APPENDICES

## 16.1 Protection of Human Subjects

Informed consent must be obtained from every subject before he enters a study. It must be given freely and not under duress. Consent must be documented by the subject or the subject's legally authorized representative signing an IRB/IEC-approved consent form. Subjects who do not speak English must be presented with a consent form written in a language that they understand. A copy of the signed consent form must be given to the subject signing it. The original must be kept in the Investigator's files and made available to Sponsor and representatives of the appropriate regulatory authority upon request. If, for any reason, subject risk is increased as the study progresses, a revised, IRB/IEC-approved consent form must be signed by the subject. Before the study begins, a sample of the consent form must be provided to the Sponsor. The appropriate regulatory authority may reject otherwise scientifically valid studies if proper informed consent has not been obtained from all subjects.

### 16.1.1 Basic Elements Of Informed Consent

Every consent form must include explanations of each of the following 20 elements:

- That the trial involves research
- The purpose of the trial
- The trial treatment(s) and the probability for random assignment to each treatment
- The trial procedures to be followed, including all invasive procedures
- The subject's responsibilities
- Those aspects of the trial that are experimental
- The reasonably foreseeable risks or inconveniences to the subject and, when applicable, to an embryo, fetus, or nursing infant
- The reasonably expected benefits; and when there is no intended clinical benefit to the subject, the subject should be made aware of this
- The alternative procedure(s) or course(s) of treatment that may be available to the subject, and their important potential benefits and risks

- The compensation and/or treatment available to the subject in the event of a trial-related injury
- The anticipated prorated payment, if any, to the subject for participating in the trial
- The anticipated expenses, if any, to the subject for participating in the trial
- That the subject's participation in the trial is voluntary and that the subject may refuse to participate or withdraw from the trial, at any time, without penalty or loss of benefits to which the subject is otherwise entitled
- That the monitor(s), the auditor(s), the IRB/IEC, and the regulatory authority(ies) will be granted direct access to the subject's original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by applicable laws and regulations and that, by signing a written informed consent form, the subject or the subject's legally acceptable representative is authorizing such access
- That the records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available; and if the results of the trial are published, the subject's identity will remain confidential
- That the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the trial
- The person(s) to contact for further information regarding the trial and the rights of trial subjects, and whom to contact in the event of a trial-related injury
- The foreseeable circumstances and/or reasons under which the subject's participation in the trial may be terminated
- The expected duration of the subject's participation in the trial
- The approximate number of subjects involved in the trial

Nothing in these regulations is intended to limit the authority of a physician to provide emergency medical care to the extent the physician is permitted to do so under applicable federal, state, or local laws.

Informed consent allows the subject to fully understand his participation and serves to protect the Investigator and Sponsor from potential negligence claims. A fully informed subject is the best protection against such claims.

The informed consent requirements in these regulations are not intended to preempt any applicable federal, state, or local laws that require additional information to be disclosed in order that informed consent be legally effective. Some states require further action on the Investigator's part concerning subject consent.

## 16.2 Requisite Documents for Approval of Study Site

Oral ifetroban sodium will be provided to the Investigators after they have submitted the following documents to the Study Monitor:

- Signed protocol
- Signed Statement of Investigator or FDA Form 1572 (if required by the regulatory agency)
- Document indicating IRB/IEC approval of the final protocol, the informed consent and/or assent and recruitment advertisement documents (to include name, address, and chairperson of the IRB/IEC)
- Blank copy of the IRB/IEC-approved informed consent document
- Signed Investigator's Agreement and Letter of Confidentiality
- Clinical Laboratory Certification and normal ranges for tests that are performed in the laboratory for study assessments
- *Curricula vitae* for the Investigator and Sub-Investigator(s) (i.e. individuals who, as part of an investigative team, will assist the investigator and make a direct and significant contribution to the data. In general, if an individual is directly involved in the performance of procedures required by the protocol, and the collection of data, that person should be listed on the 1572).
- Financial disclosure Form FDA 3454 (any study FDA relies on to establish that the product is effective or any study in which a single investigator makes a significant contribution to the demonstration of safety).

## 16.3 Responsibilities and Obligations of Investigators and Sponsors

### 16.3.1 Sponsor/Study Monitor

The CPI Study Monitor will:

**Conduct a pre-investigation Site Selection Visit and/or Study Initiation Visit to:**

- Establish the acceptability of the facility and record the visit in a written report (i.e., memorandum or form).

- Discuss with the Investigator the proposed clinical trial and supply draft CRFs, the Investigator's Brochure, and the draft protocol for review and approval.

- Discuss with the Investigator the regulatory requirements with respect to informed consent, IRB/IEC approval of the trial, the protocol, protocol amendments, and changes to the informed consent document.

- Discuss with the Investigator the timing of interim and final reports to the Study Monitor and obligation to supply the Study Monitor with copies of all study-related documents (including IRB/IEC approval, IRB/IEC charter or equivalent, membership and qualifications, protocol amendments, informed consent documents, and consent changes), CRFs, CRF changes, and all pertinent correspondence to and from the IRB/IEC.

**Conduct periodic on-site visit(s) to:**

- Assure adherence to the protocol.

- Review CRFs and hospital records for accuracy and completeness of information.

- Examine pharmacy or other IMP storage and dispensing records for documentation of quantity and date of receipt of investigational drug, dispensation and accountability data for product administration to each subject, loss of materials, contamination, and unused supplies.

- Record and report (summarize) observations on the progress of the trial and continued acceptability of the facilities, and prepare an on-site visit report.

- Review Investigator files for required documents, (e.g., protocols; protocol amendments; Investigator's Brochure; Study Procedures Manual; IRB/IEC approval of protocols, amendments, and informed consent documents; IRB/IEC charter and membership; and communications to and from the IRB/IEC and the Study Monitor.

## 16.3.2 Investigator

**Institutional Review Board/Independent Ethics Committee**

The Investigator must assure the Study Monitor in writing that the Institutional Review Board/Independent Ethics Committee (IRB/IEC):

- Meets FDA 21CFR 56 and/or ICH regulations as defined in ICH E 63: Institutional Review Board/Independent Ethics Committee (as applicable).
- Has the authority delegated by the parent Institution and found in the IRB/IEC by-laws, operation guidelines, or charter to approve or disapprove clinical trials and protocols, including informed consent and other documents (e.g., protocol amendments and information to be supplied to subjects concerning informed consent).
- Complies with proper personnel make-up of the Board.
- Convenes meetings using acceptable rules of order for making decisions, recording such decisions, and implementing them.
- Maintains files that contain (a) documentation of its decisions, such as are found in IRB/IEC minutes and correspondence, (b) written guidelines or by-laws governing IRB/IEC functions, (c) protocol, (d) protocol amendments, (e) approved informed consent document and information to be supplied to the subject, and (f) correspondence between the IRB/IEC and Investigator (e.g., consent changes, protocol amendments).

**Informed Consent of Human Subjects**

The Investigator must assure the Study Monitor in writing that the informed consent document for a subject:

- Meets FDA 21CFR part 50 and/or ICH regulations as defined in ICH E6 4.8: Informed Consent of Trial Subjects (as applicable).
- Has been approved by the IRB/IEC, including (when required) information to be given to the subject regarding the trial in which he is enrolled.
- Includes the basic elements and any additional elements of informed consent that are appropriate.

- Has been signed by both the subject and the Investigator or designee, and a copy has been given to the subject.

- May be provided to the subject in the "short form" informed consent document with written information as an alternative.

**Storage and Dispensing of Product Supplies**

The Investigator (or Pharmacist) must assure the Study Monitor in writing that:

- Adequate and accurate written records show receipt and disposition of all product supplies, including dates, serial or lot numbers, quantities received, and each quantity dispensed, administered, or used, with identification of each subject.

- Purpose and reasons are given in written records for product disposal (e.g., the amount contaminated, broken, or lost) and the quantity that was returned to the Sponsor.

**Case Report Forms**

The Investigator must assure the Study Monitor in writing that:

- The completed CRF accurately reflects the hospital records for each subject.

- The CRFs and hospital records will be accessible to the Clinical Monitor during on-site visits.

**Files and Records**

The Investigator must assure the quality, integrity, and content of his files, which will be subject to audit by the Study Monitor and the appropriate regulatory authority inspectors. The files must contain, as minimum:

- Correspondence to and from the IRB/IEC and to and from the Clinical Monitor.

- Documents including the following:

    - IRB/IEC-approved protocols.

    - IRB/IEC-approved protocol amendments.

    - IRB/IEC-approved informed consent/assent documents and information to be supplied to the subject.

- IRB/IEC-approved recruitment advertisement(s)
- IRB/IEC charter, membership, and qualifications of each member.

- Clinical supplies records including the following:
  - Receipt, date and quantity, and batch or lot number.
  - Disposition dates and quantity administered to each subject.
  - Inventory records.

Documents and records must be retained by the Investigator for a period of two years following the date a marketing application is approved for the product for the indication for which it is being investigated, **OR** If no application is to be filed or if the application is not approved for such indication, until two years after the investigation is discontinued and the appropriate regulatory authority is notified.

## 16.4 22-item Sino-nasal Outcome Test (SNOT-22)

Below you will find a list of symptoms and social/emotional consequences of your rhinosinusitis. We would like to know more about these problems and would appreciate you answering the following questions to the best of your ability. There are no right or wrong answers, and only you can provide us with this information. Please rate your problems as they have been over the past two weeks. Thank you for your participation. Do not hesitate to ask for assistance if necessary.

| 1. Considering how severe the problem is when you experience it and how often it happens, please rate each item below on how "bad" it is by circling the number that corresponds with how you feel using this scale: → | No Problem | Very Mild Problem | Mild or slight Problem | Moderate Problem | Severe Problem | Problem as bad as it can be | | 5 Most Important Items |
|---|---|---|---|---|---|---|---|---|
| **1. Need to blow nose** | **0** | **1** | **2** | **3** | **4** | **5** | | ○ |
| **2. Nasal Blockage** | **0** | **1** | **2** | **3** | **4** | **5** | | ○ |
| **3. Sneezing** | **0** | **1** | **2** | **3** | **4** | **5** | | ○ |
| **4. Runny nose** | **0** | **1** | **2** | **3** | **4** | **5** | | ○ |
| **5. Cough** | **0** | **1** | **2** | **3** | **4** | **5** | | ○ |
| **6. Post-nasal discharge** | **0** | **1** | **2** | **3** | **4** | **5** | | ○ |
| **7. Thick nasal discharge** | **0** | **1** | **2** | **3** | **4** | **5** | | ○ |
| **8. Ear fullness** | **0** | **1** | **2** | **3** | **4** | **5** | | ○ |
| **9. Dizziness** | **0** | **1** | **2** | **3** | **4** | **5** | | ○ |
| **10. Ear pain** | **0** | **1** | **2** | **3** | **4** | **5** | | ○ |
| **11. Facial pain/pressure** | **0** | **1** | **2** | **3** | **4** | **5** | | ○ |
| **12. Decreased Sense of Smell/Taste** | **0** | **1** | **2** | **3** | **4** | **5** | | ○ |
| **13. Difficulty falling asleep** | **0** | **1** | **2** | **3** | **4** | **5** | | ○ |
| **14. Wake up at night** | **0** | **1** | **2** | **3** | **4** | **5** | | ○ |
| **15. Lack of a good night's sleep** | **0** | **1** | **2** | **3** | **4** | **5** | | ○ |
| **16. Wake up tired** | **0** | **1** | **2** | **3** | **4** | **5** | | ○ |
| **17. Fatigue** | **0** | **1** | **2** | **3** | **4** | **5** | | ○ |
| **18. Reduced productivity** | **0** | **1** | **2** | **3** | **4** | **5** | | ○ |
| **19. Reduced concentration** | **0** | **1** | **2** | **3** | **4** | **5** | | ○ |
| **20. Frustrated/restless/irritable** | **0** | **1** | **2** | **3** | **4** | **5** | | ○ |
| **21. Sad** | **0** | **1** | **2** | **3** | **4** | **5** | | ○ |
| **22. Embarrassed** | **0** | **1** | **2** | **3** | **4** | **5** | | ○ |

2. Please mark the most important items affecting your health (maximum of 5 items)_____ ↑

SNOT-22 Developed from modification of SNOT-20 by National Comparative Audit of Surgery for Nasal Polyposis and Rhinosinusitis Royal College of Surgeons of England.

## 16.5 PNIFR Methodology

Per Celikel 2013:

Traditional NIFR measurements can yield highly variable results. However, assessment of the rate of peak nasal inspiratory flow (PNIF) has recently been shown to be an inexpensive, simple and fast method with good reproducibility.

The PNIF meter is simply an inverted mini-Wright flow meter attached to an airtight face mask. The PNIF is then measured using a Youlten meter (or similar) in liters per minute.

All subjects should be instructed on how to use the Youlten meter properly. All subjects should be seated during testing and encouraged to inhale as hard and fast as they can through the mask while keeping the mouth closed and starting from the end of a full expiration. Two individual NIFR measurements will be taken at all study time points. The two measurements within 5% of each will be recorded. If the measurements are not within 5% of each other, a third measurement will be made and recorded.

## 16.6 Total Nasal Symptom Score (TNSS)

| Please answer all the questions to the best of your ability twice daily, once in the morning after waking up and a second time before bedtime. | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **0 = NONE 1 = MILD 2 = MODERATE 3 = SEVERE** | | | | | | | | |
| | Date: | | Date: | | Date: | | Date: | |
| | AM | PM | AM | PM | AM | PM | AM | PM |
| Please rate how your nasal **congestion** has been over the past 12 hours: | | | | | | | | |
| Please rate how your **runny nose** has been over the past 12 hours: | | | | | | | | |
| Please rate how your **nasal itching** has been over the past 12 hours | | | | | | | | |
| Please rate how your **sneezing** has been over the past 12 hours: | | | | | | | | |
| Please rate how difficult has it been with nasal symptoms to **sleep** or go about your **day's activities**: | | | | | | | | |

## 16.7 Asthma Control Questionnaire –7 (ACQ-7)

Please answer questions 1-6. Circle the number of the response that best describes how you have been during the past week.

1. On average, during the past week, how often were you woken by your asthma during the night?
   0 Never
   1 Hardly ever
   2 A few times
   3 Several times
   4 Many times
   5 A great many times
   6 Unable to sleep because of asthma

2. On average, during the past week, how bad are your asthma symptoms when you wake up in the morning?
   0 No symptoms
   1 Very mild symptoms
   2 Mild symptoms
   3 Moderate symptoms
   4 Quite severe symptoms
   5 Severe symptoms
   6 Very severe symptoms

3. In general, during the past week, how limited were you in your activities because of your asthma?
   0 Not limited at all
   1 Very slightly limited
   2 Slightly limited
   3 Moderately limited
   4 Very limited
   5 Extremely limited
   6 Totally limited

4. In general, during the past week, how much shortness of breath did you experience because of your asthma?
   0 None
   1 A very little
   2 A little
   3 A moderate amount
   4 Quite a lot
   5 A great deal
   6 A very great deal

5. In general, during the past week, how much time did you wheeze?
   0 Not at all
   1 Hardly any of the time
   2 A little of the time
   3 A moderate amount of the time
   4 A lot of the time
   5 Most of the time
   6 All the time

6. On average, during the past week, how many puffs/inhalations of short-acting bronchodilator (eg. Ventolin) have you used each day?
   0 None
   1 1-2 puffs/inhalations most days
   2 3-4 puffs/inhalations most days
   3 5-8 puffs/inhalations most days
   4 9-12 puffs/inhalations most days
   5 13-16 puffs/inhalations most days
   6 More than 16 puffs/inhalations most days

7. (To be completed by staff)

   FEV, % predicted:
   Points
   0 >95% predicted
   1 90-95% predicted
   2 80-89% predicted
   3 70-79% predicted
   4 60-69 predicted
   5 50-59% predicted
   6 <50% predicted

Points assigned = _____

Scoring: Sum points from all questions 1-7. Divide this sum by 7.

If question 7 is not available, divide by 6.

ACQ score = _____

Juniper 1999

## 16.8 Adult Equipotent Daily Doses of Inhaled Glucocorticosteroids

| Drug | Low Daily dose (µg) | Medium Daily dose (µg) | High Daily dose (µg) |
|---|---|---|---|
| Beclomethasone dipropionate – CFC | 200-500 | >500-1000 | >1000-2000 |
| Beclomethasone dipropionate – H FA | 100-250 | >250-500 | >500-1000 |
| Budesonide | 200-400 | >400-800 | >800-1600 |
| Ciclesonide | 80-160 | >160-320 | >320-1280 |
| Flunisolide | 500-1000 | >1000-2000 | >2000 |
| Fluticasone propionate | 100-250 | >250-500 | >500-1000 |
| Mometasone furoate | 200 | ≥400 | ≥800 |
| Triamcinolone acetonide | 400-1000 | >1000-2000 | 2000 |

Bachert 2016

## 16.9 Self-assessment of Treatment (Optional)

We would like to better understand your opinion on the treatment you received during the trial. Please, answer the following question. Thank you for your cooperation.

***Could you tell us about your opinion regarding the treatment you had during the trial? What did you like or dislike about the treatment?***