APPROVAL PAGE

DOCUMENT:	Statistical Analysis Plan
Number:	CPI-IFE-006
Title:	A Phase 2 Multicenter, Double-blind, Randomized, Placebo-Controlled Trial to Evaluate Oral Ifetroban in Subjects with Symptomatic Aspirin Exacerbated Respiratory Disease (AERD)
SAP DATE:	V1.9/ 21 Sept 2017
SPONSOR:	Cumberland Pharmaceuticals Inc.
PREPARED BY:	

APPROVERS: _____

CUMBERLAND® PHARMACEUTICALS

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1. INTRODUCTION

This Statistical Analysis Plan (SAP) is based on study procedures and analyses described in the protocol (dated 24 January 2017). Table shells and mock listings corresponding to the contents of this document will be included with the final version. This document, with table shells and mock listings, will be reviewed prior to any unblinded analyses, and revised if necessary.

2. LIST OF ABBREVIATIONS

Term	Definition
ACQ	Asthma Control Questionnaire
AE	Adverse Event
AERD	Aspirin Exacerbated Respiratory Disease
ANCOVA	Analysis of Covariance
BMI	Body Mass Index
CFB	Change From Baseline
CPI	Cumberland Pharmaceuticals Inc.
CRF	Case Report Form
FeNO	Fractional Exhaled Nitric Oxide
FEV1	Forced Expiratory Volume in 1 second
INR	International Normalized Ratio
ITT	Intent-to-Treat
kg	Kilogram
LOCF	Last Observation Carried Forward
LS	Least Squares
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
mL	Milliliter
NRI	Non-Responder Imputation
PCFB	Percent Change From Baseline
PP	Per Protocol
PNIFR	Peak Nasal Inspiratory Flow Rate
PT	MedDRA Preferred Term
PT	Prothrombin Time

QoL	Quality of Life
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SNOT	Sino-Nasal Outcome Test
SOC	MedDRA System Organ Class
TEAE	Treatment-Emergent Adverse Event
TNSS	Total Nasal Symptom Score
TPr	Thromboxane Prostanoid Receptor
UPSIT	University of Pennsylvania Smell Identification Test

3. STUDY OBJECTIVES

3.1 Primary Objective

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.

3.2 Secondary Objectives

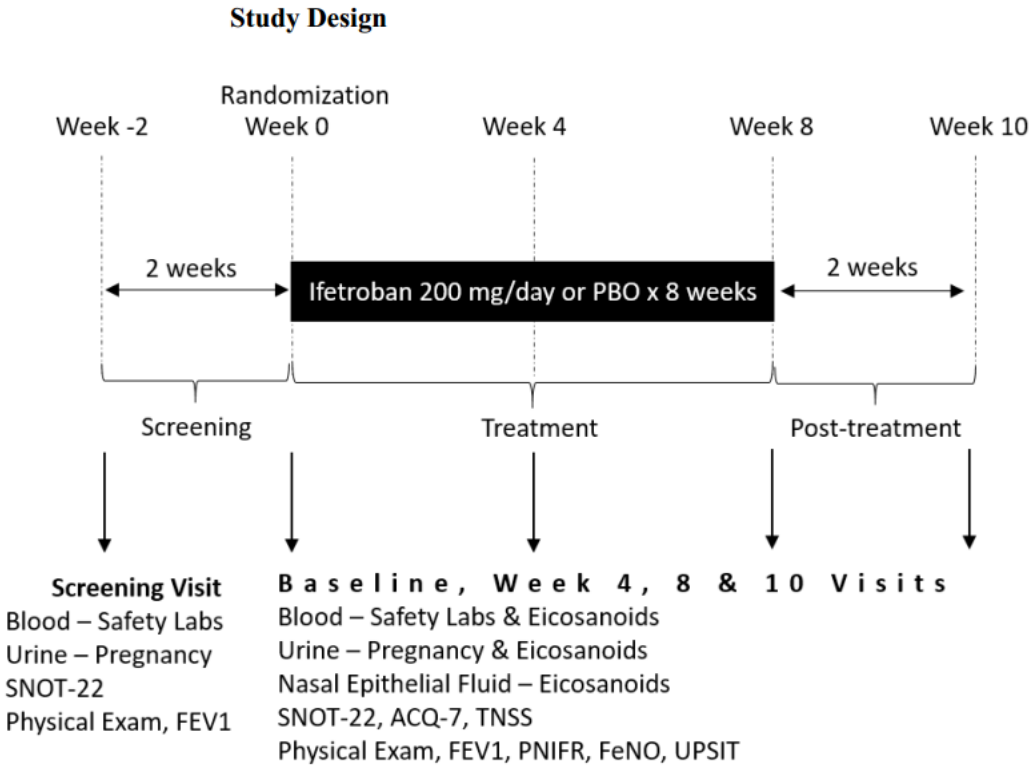
- Evaluate the effect of ifetroban on asthma symptoms by forced expiratory volume 1 (FEV1) compared to baseline.
- Assess nasal symptoms and QoL using the peak Nasal Inspiratory Flow Rate (PNIFR), University of Pennsylvania Smell Identification Test (UPSIT), fractional exhaled nitric oxide (FeNO), Asthma Control Questionnaire (ACQ) - 7 and Total Nasal Symptom Score (TNSS)
- 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.
- Evaluate the pharmacodynamic effects of TPr blockade on eicosanoids and eosinophil count.

4. STUDY DESIGN

4.1 General Study Design and Plan

This is a multicenter randomized, double-blind, placebo-controlled Phase 2 study to evaluate oral ifetroban administered daily for eight weeks in symptomatic AERD subjects. The clinical study will be conducted with 3 periods:

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



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

4.2 Study Population

Approximately 76 subjects are to be randomized into two treatment groups with 38 subjects per group.

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 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 two weeks of starting treatment by demonstrating a score of at least 20 on the SNOT – 22

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, 5-lipoxygenase inhibitors (e.g. zileuton) and leukotriene receptor antagonists (e.g. montelukast) 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 2 weeks before starting treatment

8. Any immunosuppressive treatment including but not limited to methotrexate, cyclosporine, mycophenolate, tacrolimus, gold, penicillamine, sulfasalazine, hydroxychloroquine, azathioprine, cyclophosphamide, and immunotherapy in the last two weeks before starting treatment (maintenance dose of allergy shots are allowed if treatment duration exceeds 12 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

4.3 Randomization and Blinding

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 once daily or matching 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 will be reported to the Sponsor immediately and fully documented in the subject's case report form.

4.4 Study Assessments

Schedule of Treatment & Events

	Screening Period	Treatment Period				Post-treatment Period
	Visit(s)	Visit	Phone Call	Visit	Visit	Visit
	Week -2 to Week 0	Week 0	Week 1	Week 4 (± 2 days)	Week 8 (± 2 days)	Week 10 (± 2 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 2 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.
FEV1= Forced Expiratory Volume in 1 Second; PNIFR= Peak Nasal Inspiratory Flow Rate; FeNO= Fractional exhaled Nitric oxide; PT= prothrombin time; INR= international normalized ratio; SNOT= Sino-nasal Outcome Test; TNSS= Total Nasal Symptom Score; ACQ-7= Asthma Control Questionnaire; UPSIT= Smell Identification Test; IMP= Investigational Medicinal Product; AE= adverse event; SAE= serious adverse event

4.5 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.

4.6 Study Variables

Efficacy Variables

- SNOT-22 score (Sino-Nasal Outcome Test)
    - Total Score = Sum of the values collected in the 22 questions collected in the database.
    - CFB (change from baseline) total score = post-treatment measurement - baseline
    - PCFB (percent change from baseline) = (post-treatment measurement – baseline)/baseline
    - Improvement in SNOT-22 (Yes or No): if CFB (SNOT-22) <0, then improvement = 'Yes'; otherwise improvement = 'No'
    - Nasal Related Subscale = sum of the following questions to calculate the subscale: "need to blow nose", "sneezing", "runny nose", "nasal obstruction", "loss of smell/taste", and "post-nasal drip",
    - Ear and Facial Related Subscale = sum of the following questions to calculate the subscale: "ear fullness", "dizziness", "ear pain", "facial pain and pressure"
    - Quality of Life Related Subscale = sum of the following questions to calculate the subscale: "difficulty falling asleep", "wake up at night", "wake up tired", "fatigue", "reduced productivity", "reduced concentration"
    - Psychologically Related Subscale = sum of the following questions to calculate the subscale: "frustrated/restless/irritable", "sad", "embarrassed"
    - CFB Nasal Related Subscale = post-treatment measurement visit - baseline
    - CFB Ear and Facial Related Subscale = post-treatment measurement visit – baseline
    - CFB Quality of Life Related Subscale = post-treatment measurement visit - baseline
    - CFB Psychologically Related Subscale = post-treatment measurement visit - baseline

- Forced Expiratory Volume 1 (FEV1)
    - FEV1 Value = Collected on the CRF. Measured as the "best effort" of the 3 collected measurements at each time point where "best effort"= Max (fev1_1, fev1_2, fev1_3)
    - CFB FEV1 = post-treatment measurement – baseline

- Peak Nasal Inspiratory Flow Rate (PNIFR)
  - PNIFR value= Measured as the “best effort” of the 3 collected measurements at each time point where “best effort”= Max(pnfr1, pnfr2, pnfr3)
  - CFB PNIFR = post-treatment measurement - baseline

- University of Pennsylvania Smell Identification Test (UPSIT)
  - UPSIT value - Calculated by staff. Found in the database.
  - CFB UBSIT= post-treatment measurement – baseline

- Fractional exhaled Nitric Oxide (FeNO)
  - FeNO value – Collected on the CRF.
  - CFB FeNO = post-treatment measurement - baseline

- Asthma Control Questionnaire (ACQ) – average of non-missing values
  - ACQ score. Calculated in database (ACQ_Score)
  - CFB ACQ = post-treatment measurement – baseline
  - Any improvement in ACQ-7 (Yes or No): If CFB ACQ<0, then improvement =’Yes’; otherwise improvement = ‘No’

- Total Nasal Symptom Score (TNSS) AM and PM measurements
  - TNSS Daily Score = sum of the 4 symptom scores (congestion, runny_nose, nasal_itching, sneezing) for both AM and PM, separately. (listed only)
  - TNSS Visit Score: The daily score for AM and PM are averaged over time between the visits separately. Baseline Visit Score for AM and PM is obtained by averaging over the screening period and the day of the baseline visit. Week 4 Visit Score is obtained by averaging over the day after the baseline visit to the day of the Week 4 visit. Week 8 Visit Score is obtained by averaging over the day after Week 4 visit to the day of the Week 8 visit. Week 10 Visit Score is obtained by averaging over the day after Week 8 visit to the day of Week 10 visit.
  - CFB TNSS Visit Score = post-treatment measurement – baseline

- Frequency and Severity of Asthma Exacerbations (Respiratory Reaction Questionnaire)
  - Subject Frequency =count the number of reports since the previous visit for each visit
  - CFB Frequency = post-treatment measurement – baseline
  - Max Severity= define the maximum severity for each subject (none, mild, moderate, or severe) over the period since the previous visit.
  - Inhaler or rescue med (number of reports) count= count the number of reports where resp_rxn_inhaler >0 OR resp_rxn_add_tx_yn=Yes
  - CFB Inhaler or rescue= post-treatment measurement – baseline

- Frequency and Severity of Chronic Sinusitis (Sinus Infection Questionnaire)
    - Antibiotic use Frequency (number of reports) count= count the number of reports over the period since the previous visit where sinus_inf_antibio=yes
    - CFB Antibiotic use= post-treatment measurement – baseline

Pharmacodynamic Variables and biomarkers

- Plasma - Data from third party vendor
    - ScD10L (pg/mL)
    - Sp_selection (ng/mL)
- Biomarkers - Data from third party vendor.
    - Urine LTE4 (ng/mg Creatinine)
    - Urine PGD-M (ng/mg Creatinine)
    - Urine TX-M (ng/mg Creatinine)
    - Plasma F2 Isoprostanes (ng/mL)
    - Serum LTB4 (ng/mL)
    - SAM-Eicosanoids PGD2 (ng/mL)
    - SAM-Eicosanoids PXA2 (ng/mL)
    - SAM-Eicosanoids F2 Isoprostanes (ng/mL)

4.7 ANALYSIS POPULATIONS

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

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.

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.

5. GENERAL STATISTICAL CONSIDERATIONS

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.

Appropriate summary statistics will be provided for categorical data (n, %) and for continuous data (n, mean, standard deviation, minimum, median, maximum). All recorded data will be listed by subject and by visit unless otherwise specified.

5.1 Handling of Dropouts or Missing Data

Missing efficacy data which are not retrievable through queries will be imputed.

NRI

Binary response efficacy variables will be imputed by treating the missing data as a failure, ie, non-responder imputation (NRI). A response variable that is calculated from a continuous variable will only be imputed using NRI, not from the imputed continuous variable.

LOCF

Missing data for continuous efficacy variables with at least one post-baseline measurement will be imputed using Last Observation Carried Forward (LOCF). Any calculated continuous variable will be imputed after its creation.

If the baseline value is missing for any variable, then the last screening value will be used.

MI

Multiple imputation (MI) will be provided as a sensitivity analysis for the primary efficacy variable (SNOT-22 Score CFB) only. Six imputations will be calculated from PROC MI. Week 8 will be imputed using week 0 and week 4 by treatment by treatment. The analysis will be performed on the 6 imputed sets which will provide 6 estimates of LS means from separate analyses of ANCOVAs (see Section 7.1).

```
proc mi data=thedata out=outds nimpute=6 seed=310
min=(-110 -110 -110 -110 -110 -110)
max=(110 110 110 110 110 110)
round=(1 1 1 1 1 1)
minmaxiter=100
noprint;
by trt;
var  SNOT22BASE  SNOT22CFB4 SNOT22CFB8;
run;
```

where SNOT22BASE is the baseline SNOT22 score and, SNOT22CFB4 and SNOT22CFB8 are the SNOT-22 Score values at Weeks 4 and 8, respectively.

The seed specified above will be used for development, but may be changed prior to unblinding; any such change will be documented. If convergence is not achieved with minmaxiter=100, then increase the number of iterations to 500. The properties of this approach, including convergence and collinearity, will be assessed prior to unblinding and may be adjusted to improve the operating characteristics.

After calculating the LS means of the two treatments and the estimated treatment difference and associated standard error from the ANCOVA, the 6 estimates can be placed in PROC MI analyze.

Code to obtain a single estimate of the treatment LS means and standard error.

```
proc mianalyze=thedata ; **Data output from proc mixed;
by trt;
modeleffects estimate; ***estimate of lsmeans for 6 sets;
stderr stderr; *** estimate of standard error for 6 sets;
run;
```

Code to obtain a single estimate p-value for the treatment difference.

```
proc mianalyze=thedata ; **Data output from proc mixed with /diff option
modeleffects diffestimate; ***estimate of the treatment difference for 6 sets;
stderr diffstderr; *** estimate of treatment difference standard error for 6 sets;
run;
```

5.2 Interim Analyses and Data Monitoring

There will be no interim analysis. Data will be monitored and queried throughout the study.

5.3 Multicenter Studies

The centers will be pooled for analysis.

5.4 Multiple Comparisons / Multiplicity

There are 2 treatment arms and 1 primary endpoint. There will be no adjustments for multiple comparisons or multiplicity.

6. SUMMARY OF STUDY POPULATION DATA

6.1 Subject Disposition

The number and percentage of subjects completing the study and terminating early, with the reason for termination, will be summarized for each treatment group and overall for the Safety Population. Summary statistics for subjects randomized, and in each study population and reasons for exclusion from the ITT and PP Populations will be provided for each treatment group and overall for all screened subjects. The percentages for the summaries of the number of subjects in each study population will be based on the number of subjects in the Safety Population. Protocol deviations will be listed.

6.2 Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized using descriptive statistics (for continuous variables) or frequency/percentage (for categorical variables), by treatment group and overall. Medical and surgical history will be listed for the Safety Population. Adverse events that are not treatment emergent (occur before treatment) will be listed by Safety Population.

6.3 Dosing and Extent of Exposure

Exposure and compliance will be summarized for the Safety Population by treatment group and overall. Comments recorded on the Compliance CRF page regarding dosing 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)/Exposure.

Summary statistics for exposure and compliance will be presented in a table with the corresponding listing for the Safety Population.

6.4 Concomitant Medications

A listing of concomitant medications will be provided for the Safety Population. Rescue medication for asthma exacerbation and antibiotic use for sinus infections will be summarized as noted above.

7 EFFICACY ANALYSES

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

7.1 Primary Efficacy Analysis

The primary analysis of interest is the CFB in SNOT-22 at week 8 on the ITT population, imputed with LOCF. Between-treatment comparison will be performed using Analysis of Covariance (ANCOVA) with SNOT- 22 at baseline and treatment in the model. The p-value associated with the difference between the treatments in least squares will determine significance. Least squares (LS) means, differences in LS means and the associated p-value, corresponding standard errors, and corresponding confidence intervals will be presented in a table. To assess sensitivity, this analysis will also be performed on the CFB SNOT-22 imputed using MI (Section 5.1).

The chart below outlines the analyses to be performed on each variable. It identifies the weeks for which the analysis will be performed for the corresponding variable, population, and type of imputation.

Variable Name	Value Type	Pop	Weeks for Analysis		Sensitivity (1)
			Summary	ANCOVA	
SNOT-22	Score Value	ITT/PP	0,4,8,10		LOCF
	Score CFB	ITT/PP	0,4,8,10	4,8,10	LOCF/MI
(1) Imputation analysis outlined in Section 5.1. LOCF=Last observation carried forward, MI=Multiple Imputation					

7.2 Secondary Efficacy Analyses

The analyses performed for the secondary efficacy variables will be combinations of summary statistics and ANCOVAs, using the normal approximation to the binomial (see Appendix A for details.) as appropriate, at specified visits presented in the table below.

The ANCOVA will include the corresponding value at Baseline as the only covariate with treatment. The LS means, standard error and p-values will be presented with corresponding the summary statistics.

Categorical variables will be analyzed using the normal approximation to the binomial distribution, assuming unequal variances. The p-value will be presented along with summary statistics.

The chart below outlines the analyses to be performed on each variable. It identifies the weeks in which the analysis will be performed for the variable of interest, the population, and the type of imputation.

Variable Name	Value Type	Pop	Weeks for Analysis			Imputation (2)
			Summary	ANCOVA	Binomial (1)	
SNOT-22	Score PCFB	ITT	0,4,8,10			LOCF
	Improvement(y/n)	ITT	0,4,8,10		4,8,10	NRI
SNOT-22 Subscale	Nasal Related	ITT	0,4,8,10			LOCF
	Ear and Facial	ITT	0,4,8,10			LOCF
	Quality of Life	ITT	0,4,8,10			LOCF
	Psychological	ITT	0,4,8,10			LOCF
	CFB Nasal Related	ITT	0,4,8,10			LOCF
	CFB Ear and Facial	ITT	0,4,8,10	4,8,10		LOCF
	CFB Quality of Life	ITT	0,4,8,10	4,8,10		LOCF
	CFB Psychological	ITT	0,4,8,10	4,8,10		LOCF
	22 Questions	ITT	0,4,8,10			LOCF
FEV1	Value	ITT	0,4,8,10			LOCF
	CFB	ITT	0,4,8,10	4,8,10		LOCF
PNIFR	Value	ITT	0,4,8,10			LOCF
	CFB	ITT	0,4,8,10	4,8,10		LOCF
UPSIT	Value	ITT	0,4,8,10			LOCF
	CFB	ITT	0,4,8,10	4,8,10		LOCF
FeNO	Value	ITT	0,4,8,10			LOCF
	CFB	ITT	0,4,8,10	4,8,10		LOCF
ACQ	Value	ITT	0,4,8,10			LOCF
	CFB	ITT	0,4,8,10	4,8,10		LOCF
	Improvement (y/n)	ITT	0,4,8,10		4,8,10	NRI

(1) Normal approximation to the Binomial
(2) Imputation analysis outlined in Section 5.1. NRI=Non responder imputation, LOCF=Last observation carried forward

Variable Name	Value Type	Pop	Analysis			
			Summary	ANCOVA	Binomial (1)	Imputation (2)
TNSS AM/PM	Visit Score	ITT	4,8,10			LOCF
	CFB Visit score	ITT	4,8,10	4,8,10		LOCF
Asthma	Reports	ITT	0,4,8,10			LOCF
	CFB Reports	ITT	0,4,8,10	4,8,10		LOCF
	Max Severity	ITT	0,4,8,10			LOCF
	Rescue report	ITT	0,4,8,10			LOCF
	CFB rescue report	ITT	0,4,8,10	4,8,10		LOCF
Sinusitis	Reports	ITT	0,4,8,10			LOCF
	CFB Reports	ITT	0,4,8,10	4,8,10		LOCF
	Max Severity	ITT	0,4,8,10			LOCF
	Antibiotic report	ITT	0,4,8,10	4,8,10		LOCF
	CFB Antibiotic report	ITT	0,4,8,10			LOCF
Plasma	ScD10L	ITT	0,4,8,10			LOCF
	Sp_selection	ITT	0,4,8,10			LOCF
Bio-Markers	LTE4	ITT	0,4,8,10			LOCF
	PGD-M	ITT	0,4,8,10			LOCF
	TX-M	ITT	0,4,8,10			LOCF
	F2 Isoprostanes	ITT	0,4,8,10			LOCF
	LTb4	ITT	0,4,8,10			LOCF
	SAM-Eicosanoids PGD2	ITT	0,4,8,10			LOCF
	SAM-Eicosanoids PXA2	ITT	0,4,8,10			LOCF
	SAM-Eicosanoids F2 Isoprostanes	ITT	0,4,8,10			LOCF

(1) Normal approximation to the Binomial
(2) Imputation analysis outlined in Section 5.1. NRI=Non responder imputation, LOCF=Last observation carried forward

7.3 Subgroup Analyses

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 analyses will be conducted for CFB SNOT-22 (imputed using LOCF) for the variables below.

Each covariate will be used in separate regression models for CFB SNOT-22, along with the treatment and interaction. The p-value for treatment and the interaction will be presented. Additional ad-hoc exploratory analyses may be provided based on the results of these analyses; any additional analyses will be presented in a separate report.

Covariate	Pop	Analysis		
		Summary	ANCOVA	ANOVA
Age	ITT		4,8,10	
Gender	ITT			4,8,10
Site	ITT			4,8,10
Race	ITT			4,8,10
Baseline SNOT-22	ITT		4,8,10	
Baseline TNSS	ITT		4,8,10	
Baseline ACQ-7	ITT		4,8,10	
LTE4	ITT	8	8	
PGD-M	ITT	8	8	
TX-M	ITT	8	8	
F2 Isoprostanes	ITT	8	8	
LtBct	ITT	8	8	
SAM-Eicosanoids PGD2	ITT	8	8	
SAM-Eicosanoids PXA2	ITT	8	8	
SAM-Eicosanoids F2 Isoprostanes	ITT	8	8	

8 SAFETY ANALYSES

8.1 Adverse Events

Adverse Events (AEs) will be summarized by frequency and percentage. AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) (Version 20.0 or later). An AE occurring between the first administration of study medication to the end of the study is considered a Treatment-Emergent Adverse Event (TEAE). All 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 (PT) as defined in MedDRA. The SOCs and PTs will be summarized in the following set of tables for the Safety Population:

- All AEs
- All AEs by maximum level of severity
- All AEs by closest attribution to the study medication.

Adverse events that occur during the screening period will be listed.

8.2 Clinical Laboratory Evaluation

Clinical laboratory assessments taken from blood sampling such as hematology, chemistry, PT and INR will be summarized and listed for the Safety Population.

Pregnancy test results and clinical laboratory values from urine samples will be listed for the Safety Population.

8.3 Vital Signs

Vital signs (heart rate, respiratory rate, systolic blood pressure, diastolic blood pressure and weight, and BMI) will be presented in a table with summary statistics by visit for the Safety Population. Height will be summarized for the Screening visit,

8.4 Physical Exam

Physical examination assessments will be listed by subject, visit and exam type. All exams will be listed for the baseline observation; Only abnormal results will be presented in the listings for the post baseline visits.

8.5 Safety Labs

Safety labs, Prothrombin Time (PT) and International Normalized Ratio (INR) and their associated CFB values will be summarized and listed.

9. CHANGES IN THE STATISTICAL METHODS FROM THOSE STATED IN THE PROTOCOL

The secondary variables will be analyzed with the ITT population only.

10 APPENDIX

Appendix A

Normal Approximation to the Binomial Distribution Test

Let n_1 and n_p denote the sample sizes and let m_1 and m_p denote the number of responses for Ifetroban (200mg/day), and Placebo, respectively. Furthermore, let $r_1 = m_1/ n_1$, and $r_P = m_P/ n_P$, denote the sample proportions for Ifetroban (200mg/day) and Placebo, respectively. Note that 'r' is used to denote proportions instead of the standard 'p' because p is being used to denote the p-value.

let

$$Z_{1P} = (r_1 - r_P)/s_{1P}$$

where

$$s_{1p} = \{r_1(1-r_1)/n_1 + r_p(1- r_p)/n_p\}^{1/2}.$$

The corresponding p-value is $p=1-\Phi(Z_{1P})$ where Φ is the standard normal distribution function and is calculated using the *PROBNORM* SAS function in the data step.