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GENERIC DRUG NAME: Senicapoc (ICA-17043)

PROTOCOL NO.: ICA-17043-17

PROTOCOL TITLE:

A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter Study to Assess the Safety and Efficacy of Two Weeks of Oral Senicapoc Administration on Allergen Challenge in Atopic Asthmatic Subjects

Study Centers:

A total of 2 centers in the United Kingdom took part in the study and enrolled subjects.

Study Initiation and Final Completion Dates:

06 October 2008 to 24 May 2009

Phase of Development:

Phase 2

Study Objectives:

The primary objectives of this study were to:

- Determine the safety and tolerability of multiple doses of senicapoc following oral administration to atopic asthma subjects;
- Characterize the effects of 14 days of senicapoc dosing on lung function response to allergen challenge and airway hyper-responsiveness to methacholine;
- Characterize the effects of 14 days of senicapoc dosing on changes in sputum inflammatory cell and cytokine profiles;
- Characterize the senicapoc plasma concentrations in atopic asthma subjects.

METHODS

Study Design:

This was a double-blind, placebo-controlled, parallel-group study in atopic asthmatic subjects. The study consisted of 3 phases: Screening, Treatment, and Follow-Up. During the screening phase, safety assessments and allergen and methacholine challenges were

performed to determine subject eligibility. A pretreatment recovery period of as little as 2 weeks but up to 6 weeks occurred between Screening Visit 2 and Day 1.

The treatment phase spanned 14 days and began on Day 1 with safety assessments, pulmonary function tests, and fraction of exhaled nitric oxide (FeNO). Following baseline assessments on Day 1, eligible subjects were randomized in a 1:1 ratio to placebo or senicapoc. After randomization subjects were administered the first loading dose of study medication in the clinic and were given instructions on the loading dose regimen to be followed during the first 3 days of the study.

Subjects returned to the clinic on the morning of Day 4 for their first set of safety assessments while on study medication and received their first maintenance dose while in the clinic. Subjects were given study medication and instructions on the maintenance dose regimen to be followed during the next 8 days.

Subjects returned to clinic on Days 13 and 14 for safety and pharmacodynamic assessments. On Day 13 subjects received their daily maintenance dose of study medication while in the clinic and underwent assessments including: vital signs, pulmonary function tests, FeNO, and allergen challenge study with assessment of the early and late asthmatic response (EAR and LAR). On Day 14 subjects received their final maintenance dose of study medication while in the clinic and underwent the following assessments: methacholine challenge (the provocative concentration in mg/mL causing a 20% decrease in forced expiratory volume at 1 second [FEV_1] from Baseline and provocative concentration in mg/mL causing a 20% decrease in FEV_1 from Baseline [PC_{20}] to methacholine), collection of induced sputum, measurement of FeNO, and selected safety assessments.

Following the Day 14 assessments subjects entered the 8 week follow-up phase of the study for wash-out of study medication, during which they were assessed for safety on Days 28 and 70. Senicapoc plasma concentrations were collected on Days 1, 4, 13, 14 and 70.

The schedule of study activities is presented in Table 1.

Table 1. Schedule of Activities

Study Activity	Screening Phase			Pre-Treatment Recovery	Treatment Phase				Follow-Up Phase	
	Screening Visit 1[a]	Screening Visit 2	Screening Visit 3	2-6 Weeks	Day 1[b]	Day 4	Day 13	Day 14	Day 28	Day 70
Informed consent	X									
Physical examinations	X				X				X	X
Medical history	X									
Hepatitis B and C screen	X									
Drug, alcohol, and cotinine/CO screening	X	X			X					
Clinical laboratory	X				X	X		X	X	X
Pregnancy tests	X	X			X	X	X	X		X
Vital signs	X				X	X	X		X	X
12-lead ECG	X				X	X	X		X	X
Pulmonary function tests	X	X			X	X	X (+1:40)			X
Allergen-skin-prick test	X[c]									
Methacholine challenge	X[d]		X					X (+2:00)		
Allergen challenge		X					X (+2:00)			
Sputum induction			X					X		
FeNO					X		X (+1:20)	X (+1:20)		
Pharmacokinetic samples for senicapoc					X	X	(+0:45, 1:30, 3, 4, 6, 8 h)	X (+24 h Day 13 dose)	X	X
Subject diaries					X	X	X	X		
Randomization										
Senicapoc dosing					X	X	X (0:00)	X (0:00)		
Adverse events	X	X	X	X	X	X	X	X	X	X
Concomitant medications					X	X	X	X	X	X

Table 1. Schedule of Activities

All times listed are in HH:MM format.
CO = carbon monoxide; ECG = electrocardiogram; FeNO = fraction of exhaled nitric oxide.
a. The procedures for Screening Visit 1 could have been completed over the course of >1 visit if necessary.
b. All Day 1 assessments were done prior to Day 1 dosing.
c. Skin prick test only required for those subjects not having documented history of positive skin test in past 12 months.
d. Methacholine challenge only required for those subjects who did not have documented history of response to methacholine challenge in the past 6 months.

Number of Subjects (Planned and Analyzed):

Approximately 30 subjects were planned for enrollment. A total of 34 subjects were randomized (17 subjects assigned to each treatment group); 31 subjects were eligible for analysis of efficacy variables in the evaluable population and 30 subjects were analyzed in the per protocol population.

Diagnosis and Main Criteria for Inclusion and Exclusion:

Male and female subjects with mild atopic asthma, aged 18-65 years who met the below criteria were eligible to participate in this study:

- Baseline (pre-bronchodilator) FEV_1 ≥70% predicted;
- Positive response on screening to skin prick test to either house dust mite, cat hair, or grass pollen;
- A positive inhaled methacholine challenge with a PC_{20} ≤8 mg/mL;
- Screening allergen challenge that demonstrated the subject experienced both EAR with a decrease in FEV_1 of ≥20% from the post saline value at least once between 5 and 30 minutes after the final concentration of allergen; and LAR with a decrease in FEV_1 of ≥15% from the post saline value on at least 3 occasions (including 2 consecutive) between 4 and 10 hours after the final concentration of allergen.

Main Exclusion Criteria: Subjects who used oral antihistamines within 1 week prior to Screening Visit 1 or any subject who experienced any allergic reaction to a drug which, in the opinion of the Investigator, suggested an increased potential for a hypersensitivity to senicapoc (eg, clotrimazole) were excluded from the study.

Study Treatment:

Senicapoc 10 mg oral tablets or placebo, which was identical to senicapoc with the exclusion of the active ingredient, were provided.

Subjects received senicapoc 80 mg twice a day (BID) for the first 3 days followed by 40 mg daily for 11 days or placebo as detailed in Table 2. Subjects were instructed to take study medication with food. On days when study medication was administered in the clinic, subjects arrived in the morning fasted and were given study medication with a light meal.

Table 2. Summary of Loading and Maintanence Doses of Senicapoc and Placebo

Study Treatment	Loading Dose Regimen	Maintanence Dose Regimen
Senicapoc	80 mg senicapoc (8 tablets) BID for 3 days (total of 48 tablets)	40 mg senicapoc (4 tablets) daily for 11 days (total of 44 tablets)
Placebo	Matching placebo (8 tablets) BID for 3 days (total of 48 tablets)	Matching placebo (4 tablets) daily for 11 days (total of 44 tablets)

BID = twice daily.

Efficacy Endpoints:

Primary Endpoint: The comparison between the senicapoc and placebo groups in the decrease in FEV_1 between 4 and 10 hours (LAR) after allergen challenge following 2 weeks of treatment.

Secondary Endpoints:

- EAR to allergen challenge;
- Measure of airway hyper-reactivity to methacholine challenge;
- Pulmonary function tests (FEV_1 and forced vital capacity);
- FeNO;
- Cell differentials and cytokine measurements from induced sputum samples.

Safety Evaluations:

Safety were assessed by observed or spontaneously reported adverse events (AEs); clinical laboratory tests included hematology, serum chemistry and urinalysis; physical examination findings; vital signs; and 12-lead electrocardiograms (ECGs).

Statistical Methods:

Safety Population: The set of subjects who received at least 1 dose of study medication (senicapoc or placebo). These subjects were analyzed by the treatment they received, regardless of the treatment to which they were randomized.

Evaluable Population: The set of subjects who received study medication for at least 13 days and who completed the primary efficacy endpoint assessment of allergen challenge on Day 13. The primary and secondary efficacy analyses were performed on subjects on this population as randomized, regardless of which treatment they received.

Per Protocol Population: The set of subjects who received study medication for at least 13 days, who completed the primary efficacy endpoint assessment of allergen challenge on Day 13, were not excluded for compliance or protocol deviation purposes, and had complete allergen challenge data (up through 10 hours post allergen challenge on both Screening Visit 2 and Day 13). The primary efficacy analysis and the EAR secondary analysis defined and they were performed on subjects from this population as randomized, regardless of which treatment they received.

Pharmacokinetic Population: The plasma pharmacokinetic (PK) analysis population consisted of those subjects who had at least 1 postdose PK blood draw.

Primary Endpoint: An analysis of covariance (ANCOVA) model was used in this analysis with treatment as a factor and the Day 1 maximum percent decrease in FEV_1 between 4 and 10 hours (LAR) as a covariate. The decrease in FEV_1 was quantified in 3 ways: maximum

percent decrease; average percent decrease; and change in area under the FEV_1 versus area under time curve (AUC).

Secondary Endpoints: All secondary endpoints were analyzed using an ANCOVA model with baseline response modeled as a continuous covariate.

Safety parameters were evaluated using descriptive statistics. No statistical analysis were performed.

RESULTS

Subjects Disposition and Demography:

A total of 87 subjects were screened of which 34 subjects were randomized (Table 3). All subjects completed at least 13 days of study medication and were included in the safety population. Day 13 and 14 efficacy assessments were performed on 31 of the 34 subjects. Two (2) subjects discontinued on Day 13 prior to efficacy assessments due to AEs of upper respiratory infections that prevented them from undergoing the allergen challenge. One (1) subject had a >10% decrease in FEV_1 following saline inhalation that prevented her from completing the allergen challenge.

Table 3. Subject Disposition (Safety Population)

Subject Disposition n (%)	Treatment Group		Total N=34
	Senicapoc N=17	Placebo N=17	
Randomized	17	17	34
Completed	16 (93%)	14 (81%)	30 (88%)
Withdrew	1 (6%)	3 (18%)	4 (12%)
Reason for withdrawal, n (%)			
AE	1 (6%)	1 (6%)	2 (6%)
Withdraw consent		1 (6%)	1 (3%)
Investigator deemed necessary		1 (6%)	1 (3%)
Analysis population n (%)			
Safety population	17 (100%)	17 (100%)	34 (100%)
Evaluable population	16 (94%)	15 (88%)	31 (91%)
Per protocol population	15 (88%)	15 (88%)	30 (88%)
Pharmacokinetic population	17 (100%)	0	17 (50%)

AE = adverse event; n = number of subjects with specified criteria; N = total number of subjects.

Randomization was balanced with 17 subjects assigned to each treatment group, 68% of subjects were female and 85% were White. Demographic and baseline characteristics were generally balanced across treatment groups (Table 4).

Table 4. Demographics and Baseline Characteristics (Safety Population)

Characteristics	Treatment Group	
	Senicapoc N=17	Placebo N=17
Gender n (%)[a]		
Male	7 (21%)	4 (12%)
Female	10 (29%)	13 (38%)
Race n (%)[a]		
White	16 (47%)	13 (38%)
Asian	0	1 (3%)
Black	1 (3%)	3 (9%)
Age, years, mean (SD)	35.3 (9.22)	31.6 (8.84)
Height, m, mean (SD)	1.7 (0.09)	1.7 (0.09)
Weight, kg, mean (SD)	74.5 (12.47)	71.6 (11.69)
FEV_1, liters, mean (SD)	3.2 (0.67)	2.8 (0.51)
Percent predicted FEV_1, %, mean (SD)	91.0 (10.07)	86.5 (10.78)
Mean (SD) FVC, liters	4.5 (0.97)	4.0 (0.73)

FEV_1 = Forced expiratory volume at 1 second; FVC = forced vital capacity; n = number of subjects with specified criteria; N = total number of subjects; SD = standard deviation.
a. Percent, the n for gender and race was based on total subject population (N = 34).

Efficacy Results:

As summarized in Table 5 the results of the ANCOVA analysis showed that none of the primary endpoint measures achieved statistical significance. However, the average decrease in FEV_1 at 4-10 hours (LAR response) was smaller for the senicapoc group (18.07%) than the placebo group (25.57%) (p=0.063) and the AUC_{4-10} for the LAR response was smaller for the senicapoc group (111.29 % change*hours) than the placebo group (153.93% change*hours) (p=0.079), demonstrating trends in favor of senicapoc. The maximum decrease in FEV_1 at 4-10 hours was also smaller for the senicapoc group (30.66%) than the placebo group (37.39%) (p=0.148).

Table 5. Summary of ANCOVA Analysis of Primary and Secondary Efficacy Parameters: Pulmonary Function Tests – Evaluable Population

Efficacy Parameter	Treatment Group		p-Value
	Senicapoc Adjusted Mean (SE) N=16	Placebo Adjusted Mean (SE) N=15	
Primary efficacy parameter			
Maximum decrease in FEV_1 4-10 hours[a] (% decrease from Baseline)	30.66 (3.1)	37.39 (3.2)	0.148
Average decrease in FEV_1 4-10 hours (% decrease from Baseline)	18.07 (2.6)	25.57 (2.7)	0.063
$AUC_{4\text{-}10}$ (% decrease in FEV_1 from Baseline ∗ hour)	111.29 (16.0)	153.9 (16.5)	0.079
Secondary efficacy parameter			
Maximum decrease in FEV_1 0-2 hours (% decrease from Baseline)	31.33 (3.5)	30.99 (3.7)	0.948
Average decrease in FEV_1 0-2 hours	17.51 (2.5)	17.29 (2.6)	0.951
$AUC_{0\text{-}2}$ (% decrease in FEV_1 from Baseline ∗ hour)	35.06 (5.0)	34.57 (5.2)	0.947
Day 14 PC_{20} (mg/dL)	1.04 (0.43)	1.24 (0.43)	0.753
Day 13 FeNO (ppb)	55.60 (7.1)	73.79 (7.9)	0.103
Day 14 FeNO (ppb)	100.3 (8.0)	95.65 (8.3)	0.692
Day 13 pulmonary function tests prior to allergen challenge			
FEV_1	3.12 (0.05)	3.08 (0.05)	0.530
FVC	4.35 (0.04)	4.32 (0.5)	0.655

ANCOVA = analysis of covariance; AUC = area under curve; FeNO = fraction of exhaled nitric oxide; FEV_1 = forced expiratory volume in 1 second; N = number of subjects in each category; PC_{20} = provocative concentration in mg/mL causing a 20% decrease in FEV_1 from Baseline; ppb = parts per billion; SE = standard error.

a. All values were adjusted means calculated from the ANCOVA model.

Among the secondary endpoints there was no evidence of an effect of senicapoc on the EAR. Differences in FeNO, a marker of airway inflammation, showed a trend in reduction at Day 13 (after study medication dosing but before the allergen challenge) for subjects randomized to senicapoc compared to placebo (adjusted means: placebo 73.8 ppb, senicapoc 55.6 ppb, p=0.103). There was no difference between groups in FeNO on Day 14, 24 hours after the allergen challenge (p=0.692). Thus, there was no evidence that senicapoc reduced the expected increase in FeNO following allergen challenge compared to placebo.

Among the other variables examined, only the percentage of sputum macrophage cells at Day 14 differed between the 2 groups (adjusted means: placebo 17.09%; senicapoc 29.48%, p=0.011) as shown in Table 6. Cytokine evaluations were performed on available sputum samples. A summary of the changes from predose (Screening Visit 3) to Day 14 for the 6 cytokines of most interest is presented in Table 7. The small sample size of subjects able to produce sputum samples for analysis during Screening Visit 3 and Day 14, and the variability of these results limited the ability to interpret changes in airway inflammation based on cytokine levels.

Table 6. Summary of ANCOVA Analysis of Sputum White Cell Differential – Evaluable Population (Subjects With Paired Data)

	Treatment Group		p-Value
	Senicapoc Adjusted Mean (SE)[a] N=9	Placebo Adjusted Mean (SE)[a] N=5	
Eosinophils (%)	32.2 (4.5)	34.9 (6.1)	0.729
Neutrophils (%)	31.6 (4.1)	42.2 (5.5)	0.153
Basophils (%)	0.03 (0.05)	0.09 (0.06)	0.395
Macrophages (%)	29.5 (2.3)	17.1 (3.2)	0.011
Lymphocytes (%)	7.2 (1.9)	5.0 (2.6)	0.508

ANCOVA = analysis of covariance; N = total number of subjects; SE = standard error.
a. All values were adjusted means calculated from the ANCOVA model.

Table 7. Summary of Sputum Cytokines - Evaluable Population (Subjects With Paired Data)

Cytokine (pg/mL)	Day	n	Senicapoc Mean (SD)	n	Placebo Mean (SD)
Eotaxin	SV3	7	3.1 (4.0)	7	10.1 (11.0)
	Day 14		1.1 (2.3)		6.0 (6.0)
IL-4	SV3	7	1.1 (1.4)	8	1.9 (2.6)
	Day 14		2.2 (3.2)		2.7 (2.4)
TNF-α	SV3	7	3.9 (6.4)	8	5.0 (7.5)
	Day 14		3.3 (3.4)		2.4 (2.1)
VEGF	SV3	8	88 (68)	8	115 (135)
	Day 14		87 (141)		61 (46)
LTB4	SV3	5	1018 (559)	6	788 (288)
	Day 14		1779 (1008)		1715 (1037)
PGD2	SV3	4	360 (115)	5	617 (249)
	Day 14		401 (151)		429 (89)

IL-4 = interleukin 4; LTB4 = leukotriene B4; n = number of subjects with specific criteria;
PGD2 = prostaglandin D2; SD = standard deviation; SV3 = Screening Visit 3;
TNF-α = tumor necrosis factor-alpha; VEGF = vascular endothelial growth factor.

Safety Results:

Serious Adverse Events (SAEs)/Deaths: No SAEs or deaths were reported during the study.

Adverse Events: An overall summary of treatment-emergent AEs (TEAEs) is provided in Table 8.

Table 8. Overall Summary of TEAEs

	Treatment Group		Total
	Senicapoc N=17	Placebo N=17	N=34
Number of subjects reporting TEAEs, n (%)	11 (65%)	13 (76%)	24 (71%)
Number of TEAEs reported	30	34	64

N = total number of subjects; n = number of subjects with specified criteria; TEAEs = treatment-emergent adverse events.

A summary of TEAEs that occurred in at least 2 subjects (6%) overall is provided in Table 9; incidence of TEAEs in safety population is presented in Table 10 and incidence of TEAEs - probably/possibly related to study treatment (safety population) are presented in Table 11.

Table 9. Summary of Most Frequent[a] TEAEs

System Organ Class Preferred Term	Number of Subjects		Number of TEAEs	
	Senicapoc N=17 n (%)	Placebo N=17 n (%)	Senicapoc	Placebo
Gastrointestinal disorders				
Dry mouth	3 (18%)	0	3	0
General disorders and administration Site Conditions				
Chest discomfort	1 (6%)	3 (18%)	1	5
Infections and Infestations				
Upper respiratory infection	2 (12%)	12 (2%)	3	2
Musculoskeletal and connective tissue disorders				
Back pain	0	2 (12%)	0	2
Nervous system disorders				
Headache	3 (18%)	7 (41%)	3	9
Dysgeusia	1 (6%)	1 (6%)	1	1
Respiratory, thoracic and mediastinal disorders				
Cough	2 (12%)	1 (6%)	2	1
Dyspnea	1 (6%)	1 (6%)	1	1
Forced expiratory volume decreased	1 (6%)	1 (6%)	1	1
Wheezing	0	2 (12%)	0	4
Skin and subcutaneous tissue disorders				
Acne	2 (12%)	1 (6%)	2	1

AEs = adverse events; N = total number of subjects; n = number of subjects with specified criteria; TEAEs = treatment-emergent adverse events.

a. Most frequent TEAEs were defined as AEs that occurred in at least 2 subjects overall.

Table 10. Incidence of TEAEs (Safety Population)

System Organ Class Preferred Term	Senicapoc N=17	Placebo N=17
Number of subjects with AEs	11 (65%)	13 (76%)
Infections and infestations	3 (18%)	3 (18%)
Influenza	1 (6%)	0 (0%)
Sinusitis	0 (0%)	1 (6%)
Upper repiratory tract infection	2 (12%)	2 (12%)
Viral upper respiratory tract infection	1 (6%)	0 (0%)
Blood and lymphatic system disorders	0 (0%)	1 (6%)
Lymphadenopathy	0 (0%)	1 (6%)
Immune system disorders	1 (6%)	0 (0%)
Seasonal allergy	1 (6%)	0 (0%)
Nervous system disorders	4 (24%)	8 (47%)
Dysguesia	1 (6%)	1 (6%)
Headache	3 (18%)	7 (41%)
Respiratory thoracic and mediastinal disorders	5 (29%)	4 (24%)
Cough	2 (12%)	1 (6%)
Dyspnoea	1 (6%)	1 (6%)
Epistaxis	0 (0%)	1 (6%)
Forced expiratory volume decreased	1 (6%)	1 (6%)
Oropharyngeal pain	1 (6%)	0 (0%)
Wheezing	0 (0%)	2 (12%)
Gastrointestinal disorders	5 (29%)	2 (12%)
Abdominal discomfort	0 (0%)	1 (6%)
Abdominal distention	1 (6%)	0 (0%)
Constipation	1 (6%)	0 (0%)
Diarrhea	1 (6%)	0 (0%)
Dry mouth	3 (18%)	0 (0%)
Dysphagia	1 (6%)	0 (0%)
Nausea	0 (0%)	1 (6%)
Paraesthesia oral	0 (0%)	1 (6%)
Salivary hypersecretion	1 (6%)	0 (0%)
Toothache	1 (6%)	0 (0%)
Skin and subcutaneous tissue disorders	2 (12%)	2 (12%)
Acne	2 (12%)	1 (6%)
Rash	0 (0%)	1 (6%)
Musculoskeletal and connective tissue disorders	1 (6%)	2 (12%)
Back pain	0 (0%)	2 (12%)
Musculoskeletal chest pain	1 (6%)	0 (0%)
General disorders and administration site conditions	2 (12%)	3 (18%)
Chest discomfort	1 (6%)	3 (18%)
Thirst	1 (6%)	0 (0%)
Injury, poisoning and procedural complications	1 (6%)	0 (0%)
Procedural pain	1 (6%)	0 (0%)

AEs = adverse events; N = total number of subjects; TEAEs = treatment-emergent adverse events.

Table 11. Incidence of TEAEs - Probably/Possibly Related to Study Treatment (Safety Population)

System Organ Class Preferred Term	Senicapoc N=17	Placebo N=17
Number of subjects with AEs	6 (35%)	6 (35%)
Nervous system disorders	1 (6%)	6 (35%)
Headache	0 (0%)	1 (6%)
Dysgeusia	1 (6%)	5 (29%)
Gastrointestinal disorders	5 (29%)	1 (6%)
Abdominal discomfort	0 (0%)	1 (6%)
Abdominal distention	1 (6%)	0 (0%)
Constipation	1 (6%)	0 (0%)
Diarrhea	1 (6%)	0 (0%)
Dry mouth	3 (18%)	0 (0%)
Paraesthesia oral	0 (0%)	1 (6%)
Salivary hypersecretion	1 (6%)	0 (0%)
Skin and subcutaneous tissue disorders	2 (12%)	0 (0%)
Acne	2 (12%)	0 (0%)
Musculoskeletal and connective tissue disorders	0 (0%)	1 (6%)
Back pain	0 (0%)	1 (6%)
General disorders and administration site conditions	1 (6%)	0 (0%)
Thirst	1 (6%)	0 (0%)

AEs = adverse events; N = total number of subjects; TEAEs = treatment-emergent adverse events.

Discontinuations due to Adverse Events: Two (2) subjects discontinued the study due to AEs of respiratory infection on Day 13, because of safety concerns of performing the allergen challenge procedure in subjects who had upper respiratory infections. Of these, 1 subject who had been randomized to senicapoc, also had a mildly elevated alanine transaminase and gamma glutamyl transaminase on the day of discontinuation. Increases in liver function tests are known to occur with *Mycoplasma pneumoniae*, a common cause of respiratory tract infections. The other subject discontinued on Day 13 prior to the allergen challenge due to a low FEV_1 following inhalation with saline.

Clinical Laboratory Test Results: There were no significant clinical laboratory, vital signs, or ECG-related TEAEs.

CONCLUSIONS:

This was the first study of senicapoc in subjects with asthma using the 80 mg BID loading dose 40 mg daily maintenance dose regimen. Senicapoc was well tolerated over 14 days and no dose-limiting AEs were identified at this dose. Three (3) findings, although not reaching statistical significance, were consistent with the hypothesis that senicapoc mediates an anti-inflammatory effect. Subjects randomized to senicapoc demonstrated a reduction in the LAR as measured by the average percent decrease in FEV_1, decrease in AUC_{4-10} and maximum percent decrease in FEV_1 following allergen challenge, compared to subjects randomized to placebo. Among the secondary endpoints, the trend in improvement in FeNO on Day 13 suggested that senicapoc may reduce inflammation in resting airways but was unable to prevent the increase in FeNO elicited by an allergen challenge. None of the other secondary endpoints indicated an effect by senicapoc. The small sample size of those

subjects able to produce sputum samples for analysis and the variability of results limited the ability to adequately assess airway inflammation by cytokine levels.

The good safety profile and the trend towards efficacy in reduction of the LAR warrants further evaluation of senicapoc in asthma subjects.