The study listed may include approved and non-approved uses, formulations or treatment regimens. The results reported in any single study may not reflect the overall results obtained on studies of a product. Before prescribing any product mentioned in this Register, healthcare professionals should consult prescribing information for the product approved in their country.

Study No: CF2110399
Title: A randomized, double blind, parallel group, placebo controlled 28 day study to investigate the safety, tolerability and pharmacodynamics of SB-656933 in subjects with cystic fibrosis.
Rationale: This study was completed to assess the safety and tolerability of 28 days repeat oral dosing with SB-656933 in subjects with cystic fibrosis (CF). There is considerable evidence to suggest that the recruitment and activation of inflammatory cells in the lung contributes significantly to the pathophysiology of CF. SB-656933 is a selective CXCR2 antagonist in development as a novel, once-daily oral anti-inflammatory agent for the maintenance treatment of CF. It is hypothesized that selective antagonism of CXCR2, by inhibiting neutrophil recruitment but not microbial killing thought to be mediated by CXCR1, would potentially restore the balance between host defense and pathogenesis mediated by neutrophils. The compound represents a novel class of agents compared with those previously approved for CF and would be expected to stabilize lung.
Phase: IIa
Study Period: 28 September 2009 to 29 December 2010
Study Design: This study was completed as a randomized, double blind, parallel group, placebo controlled multi-centre investigation. All subjects attended a screening visit (Visit 1) at which time their eligibility for study inclusion was assessed. Eligible subjects were randomized to receive study medication orally for 28 days on Day 1 (Visit 2b). Subjects completed assessments on Day -7 to Day -4 (Visit 2a), then Day 1 (Visit 2b), Day 14 (Visit 3), Day 21 (Visit 4) and Day 28 (Visit 5) during the treatment phase. Subjects also returned for a follow-up visit (Visit 6) approximately 7 to 14 days after last dose of study medication.
Centres: Sixteen (16) centers in the United States of America; 6 centers in Germany; 5 centers in France; 3 centers in Israel; and 1 center in Canada.
Indication: Cystic fibrosis
Treatment: Subjects were randomized to receive either 20 mg or 50 mg SB-656933 or placebo oral tablets for 28 days.
Objectives: The primary objective of this study was to assess the safety and tolerability of 28 days repeat dosing with SB-656933 in subjects with cystic fibrosis (CF).The secondary objectives for this study were to evaluate the effects of 28 days of treatment with SB-656933 in subjects with CF compared with placebo on sputum microbiology, sputum neutrophils, sputum markers of inflammation, pulmonary function assessed by spirometry, systemic markers of inflammation in serum, Daily Respiratory Symptom Diary for Cystic Fibrosis (Self Reported Version), and repeat dose pharmacokinetics (PK) of SB-656933 in cystic fibrosis subjects. The results for the primary objective only are presented in this document.
Statistical Methods: Sample size: The sample size was primarily based on feasibility since it was not viable to power the study on the primary endpoints of safety and tolerability, or with respect to non-inferiority of qualitative microbiological analysis of sputum. A sufficient number of subjects were enrolled such that approximately 100 subjects completed dosing and critical assessments. **Populations of Interest:** The 'All Subjects Population' included 146 subjects and was defined as all subjects who received at least one dose of study medication. The 'Per Protocol Population' included 142 subjects and was defined as subjects in the 'All Subjects' population who did not have protocol deviations. The 'PK Population' included 85 subjects and was defined as subjects in the 'All Subjects' population for whom a pharmacokinetic sample was obtained and analyzed. **Safety and tolerability:** Safety data were listed and summarized; no formal statistical analysis was performed. **Pharmacodynamics/Biomarkers:** Adjusted means for each treatment were presented with 90 % confidence intervals for $\log_e$-transformed pharmacodynamic/biomarker data (including sputum differential cell counts, sputum inflammatory biomarkers, serum and plasma inflammatory biomarkers and lung function data), with point estimates of the treatment differences (SB-656933 dose vs. placebo) and associated 90 % confidence intervals were calculated (using the pooled estimate of variance) for Day 28. Sputum inflammatory biomarkers [Neutrophil Elastase (NE) and Myeloperoxidase (MPO) - both adjusted for total protein, free DNA and PGP (the collagen peptide)], serum inflammatory biomarkers (CC-16, CRP, CXCL8 (IL-8), MMP-8 and MMP-9) and plasma inflammatory biomarkers (fibrinogen) were analyzed in a similar way to that described for the Sputum Differential Cell Count data, with data below the quantification limit (BQL) imputed with 1/2 lower limit of quantification (LLQ) value, and data above the quantification limit (AQL) imputed with the AQL limit value. An exploratory TOBIT analysis was performed on biomarkers CRP, CXCL-8, Free DNA, MPO, NE and SP-D, as these data incurred values below the quantification limit (BQL) and/or AQL. Lung function data (change from baseline FEV_1 and FVC) were analyzed in a similar way to that described for Percent sputum neutrophils, with the

statistical analysis for change from baseline lung function measures including day and baseline as fixed effects in the model as well. The response was the change from baseline lung function measures. **Pharmacokinetics:** Pharmacokinetic parameters were derived using non-compartmental methods. **Health Outcomes Assessments:** Categorical variables were summarized for the Daily Respiratory Symptoms Diary for Cystic Fibrosis by the number and percentage of subjects in each category.

Study Population: Subjects with cystic fibrosis.

Number of Subjects	**Placebo (n=61)**	**SB-656933 20 mg (n=44)**	**SB-656933 50 mg (n=41)**
Number of subjects randomized and received first dose of study medication, N:	61	44	41
Number of subjects included in All subjects (safety) population, n (%):	61 (100%)	44 (100%)	41 (100%)
Number of subjects included in PK population, n (%):	N/A	44 (100%)	41 (100%)
Number of subjects completed as planned, n (%):	56 (92%)	38 (86%)	39 (95%)
Number of subjects withdrawn (any reason), n (%):	5 (8%)	6 (14%)	2 (5%)
Number of subjects withdrawn for SAE, n (%):	2 (3%)	2 (5%)	2 (5%)
Number of subjects withdrawn for AE, n (%):	1 (2%)	4 (9%)	0
Reasons for subject withdrawal, n (%)			
Lost to follow-up	0	1 (2%)	0
Adverse events	1 (2%)	4 (9%)	0
Protocol deviation	2 (3%)	1 (2%)	0
Other	2 (3%)	0	2 (5%)
Demographics			
Age in Years, Mean (Min.-Max.)	29.5 (18-54)	32.9 (18-70)	31.3 (18-63)
Sex, n (%)			
Female:	22 (36%)	16 (36%)	17 (41%)
Male:	39 (64%)	28 (64%)	24 (59%)
Weight, Mean (SD)	65.0 (15.17)	66.2 (13.01)	64.9 (13.21)
Race, n (%)			
African American/African Heritage	2 (3%)	0	0
White – Arabic/North African Heritage	2 (3%)	0	0
White – White/Caucasian/European Heritage	57 (93%)	43 (98%)	41 (100%)
Mixed race	0	1 (2%)	0

Safety results: Adverse event (AE) and serious adverse event (SAE) data were collected from first dose of study medication and continued until follow up visit completion. Adverse Events greater than 5 % for the 'Per Protocol' population were the same as AEs greater than 5 % for the 'All Subjects' population, with the exception of no reports of pruritus with Placebo, and one less report of cough with SB-656933 20 mg. There were no clinically meaningful findings following review of clinical laboratory investigations for any subject in this study.

System Organ Class Preferred Term	**Placebo (N=61)**	**SB-656933 20 mg (N=44)**	**SB-656933 50 mg (N=41)**
ANY EVENT	46 (75%)	32 (73%)	32 (78%)
Respiratory, thoracic and mediastinal disorders			
Cough	12 (20%)	5 (11%)	7 (17%)
Sputum increased	9 (15%)	2 (5%)	2 (5%)
Oropharyngeal pain	4 (7%)	1 (2%)	3 (7%)
Haemoptysis	1 (2%)	4 (9%)	2 (5%)
Nasal congestion	3 (5%)	0	3 (7%)
Wheezing	4 (7%)	1 (2%)	1 (2%)
Pulmonary congestion	0	1 (2%)	2 (5%)
Rales	1 (2%)	2 (5%)	0
Rhinorrhoea	0	1 (2%)	2 (5%)
Nervous system disorders			
Headache	16 (26%)	13 (30%)	7 (17%)
Dizziness	2 (3%)	3 (7%)	1 (2%)
Sinus headache	0	4 (9%)	0

General disorders and administration site conditions			
Chest discomfort	5 (8%)	3 (7%)	5 (12%)
Fatigue	5 (8%)	3 (7%)	1 (2%)
Pyrexia	0	4 (9%)	2 (5%)
Pain	2 (3%)	2 (5%)	1 (2%)
Irritability	0	3 (7%)	0
Infections and infestations			
Infective pulmonary exacerbation of cystic fibrosis	5 (8%)	4 (9%)	5(12%)
Nasopharyngitis	3 (5%)	4 (9%)	4 (10%)
Gastrointestinal disorders			
Diarrhoea	3 (5%)	3 (7%)	3 (7%)
Abdominal pain	2 (3%)	4 (9%)	1 (2%)
Nausea	2 (3%)	3 (7%)	0
Vomiting	3 (5%)	1 (2%)	1 (2%)
Constipation	1 (2%)	1 (2%)	2 (5%)
Flatulence	1 (2%)	0	2 (5%)
Abdominal discomfort	0	2 (5%)	0
Investigations			
Pulmonary function test decreased	2 (3%)	3 (7%)	0
C-reactive protein increased	1 (2%)	0	2 (5%)
Musculoskeletal and connective tissue disorders			
Arthralgia	2 (3%)	2 (5%)	0
Back pain	1 (2%)	2 (5%)	1 (2%)
Musculoskeletal pain	0	0	2 (5%)
Skin and subcutaneous tissue disorders			
Pruritus	1 (2%)	2 (5%)	1 (2%)

Serious Adverse Events, n (%):

System Organ Class **Preferred Term**	**Placebo** **(N=61)**	**SB-656933** **20 mg (N=44)**	**SB-656933** **50 mg (N=41)**
ANY EVENT	2 (3%)	2 (5%)	2 (5%)
Infections and infestations			
Any event	2 (3%)	1 (2%)	1 (2%)
Infective pulmonary exacerbation of cystic fibrosis	2 (3%)	1 (2%)	1 (2%)
Sinusitis	1 (2%)	0	0
Gastrointestinal disorders			
Any event	0	1 (2%)	0
Intestinal obstruction	0	1 (2%)	0
Respiratory, thoracic and mediastinal disorders			
Any event	0	0	1 (2%)
Haemoptysis	0	0	1 (2%)