Study No.: MKI113006
Title: A Randomised, Double-blind, Placebo-controlled, Parallel-Group, Multi-centre, Dose Ranging Study to Evaluate the Efficacy and Safety of Losmapimod (GW856553) Tablets Administered Twice Daily compared with placebo for 24 weeks in Adult Subjects with Chronic Obstructive Pulmonary Disease (COPD)
Rationale: Impaired physical activity plays an important role in the morbidity and mortality associated with COPD and improving exercise tolerance is a main goal of treatment. This study evaluated the effect of three doses of losmapimod compared with placebo, on six minute walking distance (6MWD) in patients with COPD.
Phase: IIb
Study Period: 04Nov2010 - 22Dec2011
Study Design: Randomised, double-blind, parallel-group, multi-centre study evaluating losmapimod 2.5mg, 7.5 mg and 15 mg BID versus placebo on six minute walking distance. Subjects were randomised to 24 weeks of treatment after a one-week run-in period. Follow-up was conducted over the telephone or at a clinic visit approximately 1 week after study completion.
Centres: 48 centres in 8 countries: Argentina, Czech Republic, Estonia, Germany, Korea, Norway, Ukraine, United States of America.
Indication: COPD
Treatment: Subjects were randomised to one of four treatments, given orally as tablets twice daily (BID): losmapimod 2.5mg; losmapimod 7.5mg; losmapimod 15mg; placebo. Subjects randomised to the 15mg BID group received losmapimod 7.5mg BID for the first 4 weeks before their dose was increased to 15mg BID.
Objectives: The primary objective was to evaluate the effect of each dose of losmapimod compared with placebo on exercise tolerance, as assessed by 6MWD.
Primary Outcome/Efficacy Variable: The primary endpoint was 6MWD following 24 weeks of treatment with losmapimod 2.5mg, 7.5 mg and 15 mg BID versus placebo treatment.
Secondary Outcome/Efficacy Variable(s): Effect of treatment with losmapimod 2.5mg, 7.5 mg and 15 mg BID versus placebo treatment on: Pulmonary function assessed by spirometry (forced vital capacity (FVC), forced expiratory volume in 1 second (FEV_1). Pulmonary function assessed by body plethysmography [inspiratory capacity (IC), residual volume (RV), functional residual capacity (FRC), total lung capacity (TLC), slow vital capacity (SVC)]. Saint George's Respiratory Questionnaire-COPD (SGRQ-C) scores. Systemic biomarkers: plasma fibrinogen and serum high sensitivity C-reactive protein (hsCRP). Number of exacerbations.
Pharmacokinetics (PK): Population PK parameters of GW856553
Statistical Methods: Sample size calculations were based on the primary endpoint of 6MWD. A study with 150 subjects randomised to each treatment arm was estimated to have 90% power to detect an increase in mean walking distance of 35m between any dose of losmapimod and placebo using a two sided 5% significance level. The primary population for all efficacy and safety endpoints was the Intent-to-Treat (ITT) population which consisted of all subjects randomised to treatment and who received at least one dose of trial medication The primary analysis of 6MWD at six months used a mixed model repeated measures analysis for the ITT population. Covariates in the model were treatment group, baseline value (of 6MWD), smoking status, history of exacerbations, region, visit, visit by baseline value, and visit by treatment group interactions. Visit was fitted as a categorical variable, the interactions terms meant that the effect of treatment group and baseline could vary at each visit. The model was used to estimate treatment differences and associated p-values and 95% confidence limits for each visit. For the secondary endpoints, plethysmography and spirometry measures, plasma fibrinogen, hsCRP and total SGRQ-C score were compared between treatments using the mixed model repeated measures analysis as for the 6MWD. Plasma fibrinogen and serum hsCRP were log transformed prior to analysis. The exacerbation rate was analysed using a generalised linear model, assuming the number of exacerbations had a negative binomial probability distribution and that its mean was related to covariate factors with a 'log link' function, with the logarithm of time followed for exacerbations as an offset variable.

Covariates in the model were treatment group, smoking status, history of exacerbations (as an ordinal variable), and region.
For PK analyses, a non-linear mixed-effect modelling approach was applied.

Study Population: Key inclusion criteria were male or female subjects aged ≥ 40 years of age with a clinical history of COPD, a post-salbutamol/albuterol forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC) ratio of ≤0.70 and a post-salbutamol/albuterol FEV_1 ≤80% of predicted normal values. All subjects had a six minute walk distance (6MWD) of <350 m, and were current or ex-smokers with a smoking history of at least 10 pack years.

	Placebo	**Losmapimod 2.5 mg**	**Losmapimod 7.5 mg**	**Losmapimod 15 mg**
Number of Subjects:				
Planned, N	150	150	150	150
Randomised and received treatment (ITT), N	153	149	151	149
Completed, n (%)	129 (84)	127 (85)	127 (84)	114 (77)
Total Number Subjects Withdrawn, N (%)	24 (16)	22 (15)	24 (16)	35 (23)
Withdrawn due to Adverse Events n (%)	8 (5)	10 (7)	12 (8)	16 (11)
Withdrawn due to Lack of Efficacy n (%)	7 (5)	2 (1)	2 (1)	6 (4)
Withdrawn for other reasons n (%)	9 (6)	10 (7)	10 (7)	13 (9)
Demographics	**Placebo**	**Losmapimod 2.5 mg**	**Losmapimod 7.5 mg**	**Losmapimod 15 mg**
N (ITT)	153	149	151	149
Females: Males	104: 49	101: 48	103: 48	105: 44
Mean Age, years (SD)	63.9 (8.6)	66.1 (8.6)	66.1 (7.8)	64.8 (9.3)
Race, n (%) White, Asian African American/African Heritage	 131 (86) 19 (12) 3 (2)	 131 (88) 16 (11) 2 (1)	 132 (87) 18 (12) 1 (<1)	 118 (79) 23 (15) 8 (5)

Primary Efficacy Results:

Week 24 6MWD (m)	**Placebo**	**Losmapimod 2.5 mg**	**Losmapimod 7.5 mg**	**Losmapimod 15 mg**
N (ITT)	153	149	151	149
Mean Baseline (SD)	297.4 (53.40)	304.1 (46.56)	303.5 (45.28)	298.3 (52.20)
Mean Week 24 (SD)	330.3 (65.94)	328.5 (53.81)	330.1 (58.23)	323.2 (70.25)
Least squares mean change from baseline (SE)	27.9±4.13	21.2±4.19	23.2±4.09	24.5±4.27
Column-placebo Difference	-	-4.7	-3.4	-6.7
95% Confidence Interval	-	(-16.1, 6.8)	(-15.1, 8.2)	(-18.2, 4.9)
p-value	-	0.422	0.564	0.260

Secondary Outcome Variables:

	Losmapimod 2.5 mg vs. placebo		**Losmapimod 7.5 mg vs. placebo**		**Losmapimod 15 mg vs. placebo**	
Week 24	**Treatment difference**	**95% CI**	**Treatment difference**	**95% CI**	**Treatment difference**	**95% CI**
Spirometry endpoints (L)						
Pre-bronchodilator FEV_1	0.004	-0.04, 0.05	0.018	-0.02, 0.06	0.015	-0.03, 0.06
Post-bronchodilator FEV_1	-0.009	-0.05, 0.03	0.020	-0.02, 0.06	0.006	-0.04, 0.05
Pre-bronchodilator FVC	-0.024	-0.22, 0.07	-0.007	-0.01, 0.08	0.043	-0.05, 0.13
Post-bronchodilator FVC	-0.028	-0.12, 0.06	0.010	-0.08, 0.10	0.035	-0.05, 0.12

Plethysmography endpoints (L)						
IC	-0.044	-0.15, 0.06	-0.053	-0.16, 0.06	-0.040	-0.15, 0.07
RV	0.138	-0.07, 0.34	0.199	-0.005, 0.40	0.132	-0.077, 0.34
FRC	0.174	-0.01, 0.36	0.196	0.011, 0.38	0.140	-0.05, 0.33
TLC	0.075	-0.12. 0.27	0.150	-0.04, 0.23	0.093	-0.11, 0.29
SVC	-0.119	-0.26, 0.02	-0.036	-0.18, 0.11	-0.033	-0.18, 0.11
SGRQ-C scores						
Total score	0.4	-2.7, 3.5	1.9	-1.2, 5.0	-1.4	-4.5, 1.8
Symptom score	1.1	-2.7, 4.9	0.9	-2.9, 4.7	1.3	-2.6, 5.1
Activity score	0.2	-3.6, 4.0	0.7	-3.1, 4.5	-2.0	-5.9, 1.9
Impact score	-0.3	-4.1, 3.4	2.2	-1.5. 5.9	-2.0	-5.8, 1.8
	Treatment/ placebo Ratio	**95% CI**	**Treatment/ placebo Ratio**	**95% CI**	**Treatment/ placebo Ratio**	**95% CI**
Systemic biomarkers						
Plasma fibrinogen	1.01	0.95, 1.07	0.96	0.90, 1.02	0.95	0.90, 1.01
Serum hsCRP	0.95	0.74, 1.22	0.81	0.64, 1.04	0.86	0.67, 1.11
COPD exacerbations						
Rate of moderate/severe exacerbations/year	1.02	0.65, 2.59	0.97	0.63, 1.51	0.71	0.44, 1.15

Pharmacokinetics Results:

Predicted losmapimod exposure, geometric mean (95% CI)	**Losmapimod 2.5 mg**	**Losmapimod 7.5 mg**	**Losmapimod 15 mg**
Area under concentration time curve (24 h) (ng.h/mL)	210 (136, 614)	629 (409, 947)	1180 (791, 1577)
Trough concentration (ng/mL)	4.92 (2.63, 11.3)	14.7 (7.92, 30.3)	26.6 (15.0, 43.3)
Average concentration (ng/mL)	8.74 (5.68, 13.1)	26.2 (17.0, 39.5)	49.1 (33.0, 65.7)
Maximum concentration (ng/mL)	13.1 (9.31, 23.3)	39.3 (26.0, 62.5)	72.5 (54.3, 107)

An on therapy adverse event (AE) was defined as an AE with onset on or after the start date of study medication but not later than one day after the last date of study medication

	Placebo	**Losmapimod 2.5 mg**	**Losmapimod 7.5 mg**	**Losmapimod 15 mg**
Most Frequent Adverse Events – On-Therapy	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Subjects with any AE(s), n(%)	93 (61)	91 (61)	84 (56)	95 (64)
COPD	37 (24)	35 (23)	38 (25)	26 (17)
Headache	13 (8)	15 (10)	11 (7)	13 (9)
Nasopharyngitis	12 (8)	8 (5)	5 (3)	9 (6)
Back pain	10 (7)	7 (5)	5 (3)	11 (7)
Pneumonia	5 (3)	1 (<1)	1 (<1)	7 (5)
Muscle spasms	4 (3)	1 (<1)	6 (4)	1 (<1)
Rhinitis	4 (3)	2 (1)	1 (<1)	3 (2)
Bronchitis	4 (3)	0	2 (1)	2 (1)
Diarrhoea	2 (1)	4 (3)	6 (4)	3 (2)
Abdominal upper pain	3 (2)	4 (3)	3 (2)	2 (1)
Urinary tract infection	1 (<1)	4 (3)	2 (1)	4 (3)
Pruritus	1 (<1)	0	4 (3)	6 (4)
Myalgia	1 (<1)	1 (<1)	4 (3)	0

Serious Adverse Events - On-Therapy
An on therapy serious adverse event (SAE) was defined as a SAE with onset on or after the start date of study medication but not later than one day after the last date of study medication

	Placebo	Losmapimod 2.5 mg	Losmapimod 7.5 mg	Losmapimod 15 mg
Subjects with any SAEs, n (%) [n considered by the investigator to be related to study medication] - includes both fatal and non-fatal events	**n (%) [related]**	**n (%) [related]**	**n (%) [related]**	**n (%) [related]**
Any event	17 (11)	12 (8)	14 (9)	15 (10)
Chronic obstructive pulmonary disease	8 (5) [0]	6 (4) [0]	2 (1) [0]	3 (2) [0]
Pneumonia	4 (3) [0]	0	1 (<1) [0]	4 (3) [0]
Angina pectoris	0	0	2 (1) [0]	0
Respiratory failure	1 (<1) [0]	0	1 (<1) [0]	1 (<1) [0]
Acute respiratory failure	0	0	0	1 (<1) [0]
Pneumothorax	0	0	0	1 (<1) [0]
Pulmonary embolism	1 (<1) [0]	0	0	0
Pulmonary oedema	0	0	1 (<1) [0]	0
Sinobronchitis	1 (<1) [1]	0	0	0
Urinary tract infection	0	0	1 (<1) [0]	0
Acute myocardial infarction	0	0	1 (<1) [0]	0
Atrial fibrillation	1 (<1) [0]	0	0	0
Atrioventricular block second degree	0	0	0	1 (<1) [0]
Myocardial infarction	0	1 (<1) [0]	0	0
Stress cardiomyopathy	0	0	0	1 (<1) [0]
Femoral neck fracture	0	0	0	1 (<1) [0]
Lower limb fracture	0	1 (<1) [0]	0	0
Spinal fracture	0	0	0	1 (<1) [0]
Ulna fracture	0	0	0	1 (<1) [0]
Spinal column stenosis	1 (<1) [0]	1 (<1) [0]	0	0
Lumbar spinal stenosis	1 (<1) [0]	0	0	0
Spinal osteoarthritis	0	0	0	1 (<1)
Eczema	1 (<1) [0]	0	1 (<1) [0]	0
Leukoplakia	1 (<1) [0]	0	0	0
Pemphigoid	0	0	1 (<1) [1]	0
Gastritis	0	0	1 (<1) [0]	0
Pancreatitis	1 (<1) [0]	0	0	0
Peptic ulcer	0	0	1 (<1) [0]	0
Chest pain	1 (<1) [0]	0	0	0
Polyp	0	1 (<1) [0]	0	0
Pyrexia	0	0	1 (<1) [1]	0
Breast cancer	0	0	1 (<1) [0]	0
Lung neoplasm malignant	1 (<1) [0]	0	0	0
Anxiety	1 (<1) [1]	0	0	0
Psychotic disorder	0	1 (<1) [0]	0	0
Deep vein thrombosis	0	0	0	1 (<1) [0]
Peripheral arterial occlusive disease	0	0	1 (<1) [0]	0
Cholecystitis	0	0	1 (<1) [0]	0
Anaphylactic reaction	0	1 (<1) [0]	0	0
Nephrolithiasis	1 (<1) [0]	0	0	0
	Placebo	**Losmapimod 2.5 mg**	**Losmapimod 7.5 mg**	**Losmapimod 15 mg**
Subjects with fatal SAEs, n (%) [n considered by the investigator to be related to study medication]	**n (%) [related]**	**n (%) [related]**	**n (%) [related]**	**n (%) [related]**

Any event	3 (2)	0	1 (<1)	2 (1)
Chronic obstructive pulmonary disease	1 (<1) [0]	0	0	0
Pulmonary oedema	0	0	1 (<1) [0]	0
Respiratory failure	0	0	0	1 (<1) [0]
Acute myocardial infarction	1 (<1) [0]	0	1 (<1) [0]	0
Sepsis	0	0	0	1 (<1) [0]
Lung neoplasm malignant	1 (<1) [0]	0	0	0

Conclusion:

There was no statistically significant difference between any dose of losmapimod and placebo on the primary endpoint, 6MWD. In the placebo, losmapimod 2.5 mg, losmapimod 7.5 mg and losmapimod 15 mg groups, 93 subjects, 91 subjects, 84 subjects and 96 subjects respectively reported adverse events. The most frequently reported events in all groups were COPD and headache. Serious adverse events (SAEs) were reported by 17, 12, 14 and 15 subjects respectively in the placebo, losmapimod 2.5 mg, losmapimod 7.5 mg and losmapimod 15 mg groups. The most commonly reported SAE in each group was COPD. Four SAEs were assessed as related to study treatment; two in the placebo group (one of sinobronchitis and one of anxiety) and two in the losmapimod 7.5 mg group (one of pemphigoid and one of pyrexia). There were six fatalities reported during the study, three in the placebo group, one in the losmapimod 7.5 mg group and two in the losmapimod 15 mg group. In the placebo group, one subject died from respiratory insufficiency following an exacerbation of COPD, one had an acute myocardial infarction which occurred one day after surgery for ileus and one had a malignant lung neoplasm, in which the presenting symptom was pulmonary embolism. The subject in the losmapimod 7.5 mg group died due to an acute myocardial infarction and associated pulmonary oedema. In the losmapimod 15 mg group, one subject, died from apparent respiratory failure, in his sleep; the cause of death for the other was reported to be sepsis resulting from bilateral purulent pleuritis and mediastinitis. None of the fatal SAEs were assessed as related to study treatment.