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.: MKI102428
Title: A 12-week, randomized, double-blind, double-dummy, placebo-controlled study to assess the anti-inflammatory activity, efficacy and safety of losmapimod in subjects with chronic obstructive pulmonary disease (COPD).
Rationale: COPD is considered to have both pulmonary and systemic inflammatory components. This study was designed to assess the anti-inflammatory activity of losmapimod compared with placeboby measuring biomarkers in both the lung and the systemic circulation.
Phase: IIa
Study Period: 17 Jan 2008 – 27 Jul 2009
Study Design: Randomized, double-blind, double-dummy, parallel group, multi-centre study in subjects diagnosed with moderate COPD. Treatment consisted of a 12-week treatment period, preceded by a 2-week run-in period and followed by a 2-week follow-up period. Eligible subjects were randomized using a 1:1:1 ratio to receive either losmapimod 7.5 mg BID, salmeterol/fluticasone propionate combination 50/500 BID (SFC) or placebo using a computer-generated permuted block schedule and were stratified by smoking status (current or former smokers).
Centres: 31 investigators in 12 countries: Estonia, Finland, Germany, Korea, Latvia, Lithuania, Netherlands, New Zealand, Russian Federation, Slovenia, South Africa and the UK.
Indication: COPD
Treatment: Study medication was administered twice daily. Patients randomized to losmapimod received a twice-daily placebo inhalation, and patients randomized to SFC received placebo tablets to match losmapimod. In addition, inhaled salbutamol was provided to be used on an "as required basis" for symptomatic relief during the Run-In period and study treatment Period.
Objectives: The primary objective was to evaluate the effects of 12 weeks of treatment with losmapimod 7.5 mg BID compared with placebo on the percentage of sputum neutrophils at 12 weeks
Primary Outcome/Efficacy Variable: Change from baseline in the percentage of sputum neutrophils at 12 weeks
Secondary Outcome/Efficacy Variable(s): Pulmonary function assessed by body plethysmography [inspiratory capacity (IC), residual volume (RV), thoracic gas volume (TGV) at functional residual capacity (FRC), total lung capacity (TLC), slow vital capacity (SVC)]. Pulmonary function assessed by spirometry (forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1). Pulmonary function assessed by impulse oscillometry (R5-R15 peripheral resistance; frequency dependent reactance indicators of reactive capacitance properties of the lung [X5, resonant frequency (Fres), AX]). Parameters measured in induced sputum (total cell count; macrophages as a percentage of total cells; absolute inflammatory cell numbers: neutrophils, macrophages, sputum weight; inflammatory

biomarkers in the supernatant: MPO and total protein).

Plasma fibrinogen and additional systemic inflammation biomarkers

Levels of ex vivo lipopolysaccharide (LPS) induced tumour necrosis factor (TNF)-α in whole blood pre-dose and 2 h post-dose at selected centres.

Levels of ex vivo sorbitol induced phosphorylation of heat shock protein 27 (pHSP27) in whole blood pre-dose and 2h post-dose at selected centres.

Statistical Methods: The planned sample size of 100 subjects per group was estimated to provide 90% power to detect an absolute reduction of 9.3% in the primary endpoint of sputum neutrophil differential cell count between losmapimod and placebo using a two sided 5% significance test. This assumed that 80% of the patients would provide data for the analysis of sputum neutrophils.

The Safety population for analysis of safety comprised of all randomized subjects who received at least one dose of study medication. Subjects were assessed according to the treatment they actually received.

The primary analysis of sputum neutrophils at Week 12 used a mixed model repeated measures analysis. Covariates in the model included treatment group, baseline value, smoking status, country, age and sex and visit, with the effect of treatment group and baseline varying at each visit. The model was used to estimate treatment differences and associated p-values and 95% confidence limits for each visit. Secondary endpoints were log-transformed where necessary and analysed using repeated measures, as described for the primary endpoint.

Study Population:

	Placebo	**Losmapimod**	**SFC 50/500**
Number of Subjects:			
Planned, N	100	100	100
Randomised, N	98	102	102
Completed, n (%)	86 (88)	86 (85)	89 (87)
Total Number Subjects Withdrawn, N (%)	12 (12)	16 (16)	13 (13)
Withdrawn due to Adverse Events n (%)	9 (9)	11 (11)	7 (7)
Withdrawn due to Lack of Efficacy n (%)	0	0	0
Withdrawn for other reasons n (%)	3 (3)	5 (5)	6 (6)
Demographics	**Placebo**	**Losmapimod**	**SFC50/500**
N (ITT)	98	101	102
Females: Males	22: 76	24: 77	31:71
Mean Age, years (SD)	61.7 (6.02)	61.9 (7.39)	62.0 (7.67)
White, n (%)	92 (95)	91 (94)	96 (96)

Primary Efficacy Results:

	Placebo	**Losmapimod**	**SFC 50/500**
Number of subjects	68	74	75
Baseline raw mean (sd)	71.2 (16.59)	71.5 (20.47)	70.7 (21.42)
Adjusted mean	75.3	74.1	73.5
Adjusted mean change from baseline (se)	3.0 (2.00)	1.8 (1.93)	1.2 (1.91)
Active treatment – placebo (se)		-1.2 (2.79)	-1.8 (2.77)
95% Confidence Interval		(-6.7, 4.3)	(-7.2, 3.7)
p-value		0.669	0.524

Secondary Outcome Variable(s):				
	Losmapimod vs Placebo		**SFC 50/500 vs Placebo**	
Sputum endpoints	**Trt Diff**	**95% CI**	**Trt Diff**	**95% CI**
% Macrophages	-0.3	(-4.9, 4.2)	1.7	(-2.9, 6.2)
	Trt Ratio	**95% CI**	**Trt Ratio**	**95% CI**
Abs. Cell Neutrophils	0.86	(0.60, 1.23)	0.84	(0.59, 1.20)
Abs. Cell Macrophages	0.94	(0.64, 1.40)	0.83	(0.56, 1.24)
Total Leukocyte Count	0.90	(0.65, 1.24)	0.86	(0.62, 1.18)
Sputum Weight (g)	0.95	(0.74, 1.22)	0.96	(0.75, 1.23)
MPO (ng/mL)	0.85	(0.66, 1.11)	1.24	(0.96, 1.62)
Total Protein (ug/mL)	0.89	(0.70, 1.14)	1.08	(0.84, 1.37)
Spirometry endpoints	**Trt Diff**	**95% CI**	**Trt Diff**	**95% CI**
FEV_1 pre bronchodilator	48	(-27, 123)	169	(94, 244)
FEV_1 post bronchodilator	23	(-47, 92)	47	(-22, 116)
FVC pre bronchodilator	87	(-23, 197)	168	(58, 278)
FVC post bronchodilator	92	(-5, 190)	67	(-30, 163)
Plethysmography endpoints (ml)	**Trt Diff**	**95% CI**	**Trt Diff**	**95% CI**
Inspiratory capacity	-36	(148, 75)	-13	(-124, 99)
Residual volume	-124	(-257, 9)	-103	(-236, 31)
Functional residual capacity	-113	(-246, 20)	-65	(-198, 68)
Total lung capacity	-132	(-269, 5)	-81	(-218, 55)
Slow vital capacity	-29	(-133, 76)	-4	(-108, 100)
Impulse oscillometry endpoints	**Trt Diff**	**95% CI**	**Trt Diff**	**95% CI**
R5-R15 pre bronchodilator (kPa/L/sec)	-0.01	(-0.03, 0.01)	-0.02	(-0.04, 0.01)
R5-R15 post bronchodilator (kPa/L/sec)	-0.01	(-0.03, 0.01)	-0.01	(-0.02, 0.01)
	Trt Ratio	**95% CI**	**Trt Ratio**	**95% CI**
AX pre bronchodilator (kPa/L)	1.02	(0.85, 1.22)	0.89	(0.75, 1.07)
AX post bronchodilator (kPa/L)	0.96	(0.81, 1.15)	0.95	(0.80, 1.14)
Biomarkers	**Trt Ratio**	**95% CI**	**Trt Ratio**	**95% CI**
Fibrinogen	0.89	(0.83,0.96)	1.02	(0.95,1.10)
SP-D	1.01	(0.93,1.10)	0.92	(0.85,1.00)
hsCRP	0.76	(0.55,1.06)	1.04	(0.75,1.43)
CCP-16	0.97	(0.91,1.03)	0.87	(0.82,0.93)
IL-6	0.81	(0.63,1.03)	1.11	(0.87,1.42)
IL-8	0.83	(0.66,1.04)	1.02	(0.82,1.28)
MMP-9	0.89	(0.73,1.07)	1.17	(0.97,1.41)
PARC	1.06	(0.90,1.25)	1.10	(0.93,1.30)
pHSP27 and TNF-α	**Trt Ratio**	**95% CI**	**Trt Ratio**	**95% CI**
Pre-dose pHSP27	0.79	(0.63,0.99)	1.34	(1.07,1.68)
Post-dose pHSP27	0.61	(0.46,0.82)	1.18	(0.89,1.55)
Pre-dose TNF-α	0.86	(0.58,1.29)	1.03	(0.69,1.53)
Post-dose TNF-α	0.56	(0.36,0.88)	0.91	(0.59,1.41)

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 N = 98	**Losmapimod N = 101**	**SFC 50/500 N = 102**
Most Frequent Adverse Events – On-Therapy	**n (%)**	**n (%)**	**n (%)**
Subjects with any AE(s), n(%)	55 (56)	67 (66)	62 (61)

Nasopharyngitis	9 (9)	11 (11)	12 (12)
Headache	16 (16)	4 (4)	4 (4)
COPD	7 (7)	5 (5)	3 (3)
Back pain	7 (7)	2 (2)	4 (4)
Diarrhoea	5 (5)	3 (3)	2 (2)
Upper respiratory tract infection	5 (5)	2 (2)	3 (3)
Arthralgia	1 (1)	0	6 (6)
Dyspnoea	5 (5)	2 (2)	0
Dizziness	0	5 (5)	1 (< 1)
Serious Adverse Events - On-Therapy **n (%) [n considered by the investigator to be related to study medication]**			
	Placebo **N = 98**	**Losmapimod** **N = 101**	**SFC 50/500** **N = 102**
Subjects with non-fatal SAEs, n (%)	4 (4%) [1 related]	2 (2%) [none related]	2 (2%) [none related]
Myocardial infarction	2 (2%)	0	0
Angina pectoris	1 (1%)	0	0
Cystitis	0	0	1 (<1%)
Infective exacerbation of COPD	1 (1%)	0	0
Pneumonia	0	1 (<1%)	0
COPD	1 (1%) [1]	1 (<1%)	0
Nephrolythiasis	0	0	1 (<1%)
Subjects with fatal SAEs, n (%)	0	0	0

Conclusion:

There was no statistically significant difference between GW856553 or SFC and placebo on the primary endpoint, percentage neutrophils in induced sputum at week 12. The overall incidence of AEs occurring during the treatment period was comparable across all three groups, 56% in the placebo group, 66% in the GW856553 group and 61% in the SFC 50/500 group. The most commonly reported AEs were headache and nasopharyngitis. A total of 8 subjects experienced SAEs during the treatment period, 4 in the placebo group, 2 in the GW856553 group and 2 in the SFC 50/500 group. Three subjects in the placebo group and both subjects in the GW856553 group were withdrawn due to their SAEs. None of the SAEs in the GW856553 group or SFC 50/500 group were considered related to study treatment by the investigators.