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.: PM1111810

Title: A randomized, double-blind, placebo-controlled study to evaluate the safety of 12 weeks of dosing with GW856553 and its effects on inflammatory markers, infarct size, and cardiac function in subjects with myocardial infarction without ST segment elevation

Rationale: This trial was designed to investigate the use of losmapimod (GW856553) for 12 weeks in the critical care setting for management of subjects presenting to the hospital with non-ST-segment elevation myocardial infarction (NSTEMI). The study endpoints included safety and tolerability, and effects of losmapimod on inflammatory markers, and infarct size. Secondary endpoints relating to cardiac function were evaluated in part by cardiac magnetic resonance imaging (MRI), in a sub-study conducted at qualified sites.

Phase: II

Study Period: 08 October 2009 – 06 March 2012

Study Design: randomized, double-blind, placebo-controlled, parallel group, multicenter

Centres: 83 centers (7 centers in Australia, 4 in Canada, 30 in Germany, 3 in India, 5 in Netherlands, 3 in Poland, 4 in Spain, 4 in the United Kingdom, 23 in the United States)

Indication: Acute coronary syndrome

Treatment:

- Group A: oral losmapimod 7.5 mg starting dose followed 12 ± 4 hours later by losmapimod 7.5 mg twice daily (BID) maintenance dose for 12 weeks (referred to as non-loading dose group).
- Group B: oral losmapimod 15 mg starting dose followed 12 ± 4 hours later by losmapimod 7.5 mg BID maintenance dose for 12 weeks (referred to as loading dose group).
- Group P: oral placebo BID for 12 weeks.

Objectives:

- To assess the safety of losmapimod in subjects with NSTEMI.
- To assess the effects of losmapimod on biomarkers of inflammation in subjects with NSTEMI over the 12 weeks of treatment.
- To assess the effects of losmapimod on infarct size and cardiac function during the peri-infarct period and during the ensuing 12 weeks of treatment.

Primary Outcome Variable(s):

No single endpoint was selected as the primary measure of success of the study, as there were three varied, but related primary goals to evaluate effects on safety, inflammation, infarct size and cardiac function. Instead, the totality of the results based on the measures of (i) safety, (ii) inflammation, and (iii) infarct size and myocardial function were evaluated:

- Safety evaluation was made by assessment of all adverse events (AE), major adverse cardiovascular events (MACE), safety laboratory tests (including liver function values), vital signs and 12-lead electrocardiogram (ECG) parameters. MACE+ was defined as all-cause death and adjudicated myocardial infarction, stroke/transient ischemic attack (TIA), heart failure or recurrent ischemia requiring urgent revascularization. Pure MACE was defined as all-cause death and adjudicated myocardial infarction or stroke/TIA.
- The primary measure of inflammation was high-sensitivity C-reactive protein (hsCRP) at Week 12.
- The primary measure of myocardial infarct size and cardiac function was cardiac troponin I (cTnI) area under concentration-time curve (AUC) over 72 hours post-randomization or until hospital discharge (whichever came first).

Secondary Outcome Variable(s):

- hsCRP during the hospitalization period and through Week 14.
- Interleukin-6 (IL-6) at 24 hours post-randomization and at Weeks 2 and 12.
- Creatine kinase MB isoenzyme (CK-MB) AUC over 72 hours post-randomization or until hospital discharge (whichever came first).
- Peak cTnI over 72 hours post-randomization or until hospital discharge (whichever came first).
- Brain natriuretic peptide (BNP) at discharge and Week 12.
- Infarct size (% of left ventricular myocardium [% of LV]) for infarct #1 by delayed contrast-enhanced MRI at Day 3-5, Week 12 and change from Day 3-5 to Week 12. The infarct region #1 was the infarct region which the MRI interpretation process identified as the primary infarct region of the index hospitalization.
- Total infarct size (% of LV), infarct size (g) - #1, and number of distinct infarct areas by MRI at Day 3-5, Week 12 and change from Day 3-5 to Week 12. The total infarct size was the combined infarct region as summarized by the MRI interpretation.
- Left ventricular ejection fraction (LVEF), left ventricular end-diastolic volume (LVEDV) and left ventricular end-systolic volume (LVESV) by MRI at Day 3-5, Week 12 and change from Day 3-5 to Week 12.
- Left ventricular mass (LV mass), regional wall motion score index and regional hyperenhancement score index by MRI at Day 3-5, Week 12 and change from Day 3-5 to Week 12.

Statistical Methods: The target total sample size was 400 evaluable subjects (i.e. subjects completing 12 weeks). The primary endpoint for evaluating effects on inflammation was the relative percent reduction in hsCRP at 12 weeks. A sample size of 150 subjects per arm in either losmapimod group versus a sample size of 100 subjects on placebo provided 90% power to detect a 36% relative reduction in hsCRP at 12 weeks for losmapimod compared to placebo. For comparison between the combined (C) losmapimod treatment groups (group A plus group B) versus placebo, the sample size of 300 (losmapimod) versus 100 (placebo) provided 90% power to detect a 33% relative reduction in hsCRP. These calculations were based on a standard deviation of 1.06 in log hsCRP and a two-sided significance level of 5%.

The primary endpoint for evaluating effects on infarct size was the relative percent reduction in cTnI AUC. A sample size of 150 subjects per arm in either losmapimod group versus a sample size of 100 subjects on placebo provided 90% power to detect a 25% relative reduction in cTnI AUC for losmapimod compared to placebo. The selected sample size provided 45% power to detect a relative reduction of 15% in cTnI AUC (considered to be the minimal clinically relevant effect). For comparison between the combined losmapimod treatment groups versus placebo, the sample size of 300 (losmapimod) versus 100 (placebo) provided 90% power to detect a 23% relative reduction in cTnI AUC. All calculations were based on a coefficient of variation (CV) of 0.77 and a two-sided significance level of 5%. No multiplicity adjustments were made.

For the MRI sub-study, the sample size of 90 subjects (30 subjects per arm) provided at least 85% power to detect a 50% relative reduction in infarct size for losmapimod compared to placebo. The selected sample size provided less than 20% power to detect a relative reduction of 20% in infarct size (considered to be the minimal clinically relevant effect). For a pooled comparison of the losmapimod arms compared to placebo, the sample size of n=60 versus n=30 on placebo provided at least 90% power to detect a 50% relative reduction in infarct size. All calculations were based on a CV of 1.05 and a two-sided significance level of 5%.

Time to event analyses for MACE endpoints (Pure MACE and MACE+) were performed using Cox's Proportional Hazard regression with treatment group as a factor. Data for subjects without a MACE event were censored at the time of last contact. Treatment effects for specified comparisons of losmapimod versus placebo were estimated via the hazard ratio (HR) and 95% confidence interval (CI).

Modelling of biomarker data (hsCRP, IL-6, cTnI, CK-MB and BNP) was performed using two types of analysis of covariance (ANCOVA) models as appropriate to the data. For repeated measures data, a repeated measures ANCOVA model was applied. Otherwise, a non-repeated measures ANCOVA model was performed. Data were log-transformed as appropriate prior to fitting the models. The repeated measures ANCOVA model included terms for treatment, visit, CK-MB strata (from randomization), treatment*visit, strata*visit, and covariates for onset time (time from onset of chest pain to pre-dose PD sampling), log(baseline), onset time*visit and log(baseline)*visit. For the non-repeated measures

ANCOVA model, visit and associated interaction terms with visit from the model described above were excluded.

From each analysis, point estimates and 95% CIs were provided for the specified comparisons of losmapimod vs placebo. The comparison of combined losmapimod group (C):P was obtained from the same analysis using the contrast 0.5*A + 0.5*B – 1*P. Adjusted geometric least squares (LS) means were provided for each treatment group. The point estimate and 95% CI were back-transformed to provide a point estimate of the ratio of losmapimod to placebo and its associated CI. A similar repeated measures model was used for the analysis of renal function variables (serum creatinine, blood urea nitrogen [BUN] and glomerular filtration rate [GFR]).

MRI parameters were primarily analysed by a repeated measures ANCOVA model, which included terms for treatment, visit, treatment*visit, and covariates of onset time (time from onset of chest pain to pre-dose PD sampling), onset time* visit, log (pre-dose cTnI), log (pre-dose cTnI)*visit.

Safety summaries and MACE endpoints were based on the Safety Population, defined as all subjects randomized to treatment, who had taken at least one dose of study medication. Subjects in the Safety Population were classified according to the treatment received. The primary population for efficacy and biomarkers was the intent-to-treat (ITT) Population, defined as all randomized subjects who received at least one dose of study medication and had at least one on-treatment assessment for one of the endpoints of hsCRP, IL-6, BNP, troponin, CK-MB, creatinine or BUN. Subjects in the ITT Population were classified according to randomized treatment. The primary population for the statistical analysis of MRI data was the MRI ITT Population, which was the subset of the ITT population who had at least one MRI scan.

No multiplicity adjustment was made. Inferences drawn from the study were based on the totality of the data, e.g. consistent trend from multiple endpoint comparisons.

Study Population:

		Losmapimod			
	Placebo	7.5 mg BID	Loading dose + 7.5 mg BID	Combined	Total
Number of Subjects:					
Planned, N	-	-	-	-	~525
Randomised, N	140	198	197	395	535
Not dosed	2	2	5	7	9
ITT, N	138	196	192	388	526
Safety, N	135	199	192	391	526
Completed, n (%)	92 (68)	121 (61)	116 (60)	237 (61)	329 (63)
Total number subjects discontinued, n (%)	43 (32)	78 (39)	76 (40)	154 (39)	197 (37)
Discontinued due to adverse events, n (%)	5 (4)	20 (10)	17 (9)	37 (9)	42 (8)
Discontinued due to lack of efficacy, n (%)	NA	NA	NA	NA	NA
Discontinued for other reasons, n (%)	38 (28)	58 (29)	59 (31)	117 (30)	155 (29)
Demographics					
N (Safety Population)	135	199	192	391	526
Females:Males	40:95	52:147	57:135	109:282	149:377
Mean age, years (SD)	63.4 (10.29)	62.6 (11.03)	64.6 (10.50)	63.6 (10.80)	63.5 (10.66)
White, n (%)	128 (95)	183 (92)	174 (91)	357 (92)	485 (93)
Asian, n (%)	4 (3)	4 (2)	9 (5)	13 (3)	17 (3)
African American/ African Heritage, n (%)	2 (1)	6 (3)	5 (3)	11 (3)	13 (2)
Native Hawaiian or Other Pacific Islander, n (%)	1 (<1)	2 (1)	3 (2)	5 (1)	6 (1)
American Indian or Alaskan Native, n (%)	0	3 (2)	0	3 (<1)	3 (<1)

The race of 1 subject in the losmapimod non-loading dose group and 1 subject in the losmapimod loading dose group are unknown.

Primary Outcome Variables:						
		Geometric Least Squares Means				
Endpoint	Treatment comparison	Losmapimod	Placebo	Ratio	95% CI	P-value
hsCRP (mg/L)						
Week 12 [a]	A : P	1.20	1.50	0.80	(0.59, 1.09)	0.15
	B : P	1.43	1.50	0.95	(0.70, 1.29)	0.74
	C : P	1.31	1.50	0.87	(0.66, 1.14)	0.32
cTnI (ng/mL)						
Average concentration over in-hospital period [b]	A : P	2.59	2.52	1.03	(0.80, 1.32)	0.83
	B : P	2.72	2.52	1.08	(0.84, 1.39)	0.56
	C : P	2.65	2.52	1.05	(0.84, 1.32)	0.65

a. The results from nominal time point were based on repeated measures of ANCOVA model.
b. The results from in-hospital period (72 hours post-randomization or until hospital discharge, whichever came first) were based on non-repeated measures of ANCOVA model.

		Losmapimod		
	Placebo N=135	7.5 mg BID N=199	Loading dose + 7.5 mg BID N=192	Combined N=391
	n (%)	n (%)	n (%)	n (%)
MACE for Total Study				
All cause death	4 (3.0)	4 (2.0)	11 (5.7)	15 (3.8)
Myocardial infarction	16 (11.9)	14 (7.0)	21 (10.9)	35 (9.0)
Heart failure	2 (1.5)	7 (3.5)	7 (3.6)	14 (3.6)
Recurrent ischemia	3 (2.2)	3 (1.5)	2 (1.0)	5 (1.3)
Stroke/transient ischemic attack	1 (0.7)	4 (2.0)	4 (2.1)	8 (2.0)
Any MACE+	23 (17.0)	28 (14.1)	34 (17.7)	62 (15.9)
Hazard ratio for losmapimod:placebo	-	0.79	1.02	0.90
95% CI	-	(0.46, 1.38)	(0.60, 1.74)	(0.56, 1.46)
Any Pure MACE	19 (14.1)	21 (10.6)	29 (15.1)	50 (12.8)
Hazard ratio for losmapimod:placebo	-	0.72	1.07	0.89
95% CI	-	(0.39, 1.34)	(0.60, 1.90)	(0.52, 1.51)

Data for additional safety related primary outcome variables are listed in the Safety results section.

Secondary Outcome Variables:					
		Geometric Least Squares Means			
Endpoint	Treatment comparison	Losmapimod	Placebo	Ratio	95% CI
hsCRP (mg/L)					
24h [a]	A : P	7.16	9.30	0.77	(0.60, 0.99)
	B : P	6.17	9.30	0.66	(0.52, 0.85)
	C : P	6.65	9.30	0.71	(0.57, 0.89)
48h [a]	A : P	7.73	13.80	0.56	(0.40, 0.78)
	B : P	6.44	13.80	0.47	(0.33, 0.65)
	C : P	7.06	13.80	0.51	(0.38, 0.69)
72h [a]	A : P	7.27	10.70	0.68	(0.45, 1.01)
	B : P	6.45	10.70	0.60	(0.40, 0.90)
	C : P	6.85	10.70	0.64	(0.45, 0.92)
Week 2 [a]	A : P	2.13	3.03	0.70	(0.48, 1.03)
	B : P	2.13	3.03	0.70	(0.48, 1.04)
	C : P	2.13	3.03	0.70	(0.50, 0.99)
Week 4 [a]	A : P	1.34	1.73	0.78	(0.55, 1.10)
	B : P	1.55	1.73	0.90	(0.63, 1.28)
	C : P	1.44	1.73	0.83	(0.61, 1.14)
Week 8 [a]	A : P	1.29	1.61	0.80	(0.58, 1.13)
	B : P	1.60	1.61	0.99	(0.71, 1.39)
	C : P	1.44	1.61	0.89	(0.66, 1.20)
Follow-up (Week 14) [a]	A : P	2.41	1.52	1.58	(1.13, 2.22)
	B : P	2.58	1.52	1.69	(1.21, 2.38)
	C : P	2.49	1.52	1.64	(1.21, 2.21)
In hospital period [b, c] (72h/DIS/EW)	A : P	7.30	11.85	0.62	(0.43, 0.88)
	B : P	6.27	11.85	0.53	(0.37, 0.76)
	C : P	6.77	11.85	0.57	(0.42, 0.78)
Average concentration over in-hospital period [b, c]	A : P	7.50	10.98	0.68	(0.51, 0.91)
	B : P	6.58	10.98	0.60	(0.45, 0.80)
	C : P	7.03	10.98	0.64	(0.50, 0.82)
Average concentration over out-of-hospital period (Week 2 to Week 12) [c]	A : P	1.85	2.42	0.77	(0.56, 1.06)
	B : P	2.03	2.42	0.84	(0.61, 1.16)
	C : P	1.94	2.42	0.80	(0.61, 1.07)

IL-6 (pg/mL)					
24h [a]	A : P	5.85	10.73	0.54	(0.43, 0.69)
	B : P	6.87	10.73	0.64	(0.50, 0.82)
	C : P	6.34	10.73	0.59	(0.48, 0.73)
Week 2 [a]	A : P	2.63	3.47	0.76	(0.59, 0.98)
	B : P	3.04	3.47	0.88	(0.68, 1.13)
	C : P	2.83	3.47	0.82	(0.65, 1.02)
Week 12 [a]	A : P	2.16	2.67	0.81	(0.65, 1.02)
	B : P	2.60	2.67	0.97	(0.78, 1.22)
	C : P	2.37	2.67	0.89	(0.73, 1.09)
cTnI (ng/mL)					
Peak concentration over in-hospital period [b, c]	A : P	3.79	3.84	0.99	(0.78, 1.25)
	B : P	4.14	3.84	1.08	(0.85, 1.36)
	C : P	3.96	3.84	1.03	(0.84, 1.27)
CK-MB (ng/mL)					
Average concentration over in-hospital period [b, c]	A : P	6.51	6.28	1.04	(0.89, 1.21)
	B : P	6.73	6.28	1.07	(0.92, 1.25)
	C : P	6.62	6.28	1.05	(0.92, 1.21)
BNP (pg/mL)					
72h/ DIS/EW [a]	A : P	65.03	70.06	0.93	(0.72, 1.20)
	B : P	64.53	70.06	0.92	(0.72, 1.18)
	C : P	64.78	70.06	0.92	(0.74, 1.16)
Week 12 [a]	A : P	36.23	49.90	0.73	(0.55, 0.96)
	B : P	40.21	49.90	0.81	(0.61, 1.07)
	C : P	38.17	49.90	0.76	(0.60, 0.98)

a. The results from nominal time point were based on repeated measures of ANCOVA model.
b. The in-hospital period was defined as 72 hours post-randomization or until hospital discharge, whichever came first.
c. The results from in-hospital and out-of hospital periods were based on non-repeated measures of ANCOVA model.

MRI Parameters						
Time point	Treatment comparison	Geometric Least Squares Means		Absolute Difference	95% CI	Relative Change (%) [a]
		Losmapimod	Placebo			
Infarct size (% of left ventricular myocardium) for infarct #1						
Day 3-5	A - P	6.39	8.31	-1.92	(-5.25, 1.41)	-23%
	B - P	5.47	8.31	-2.84	(-6.29, 0.62)	-34%
	C - P	5.93	8.31	-2.38	(-5.44, 0.69)	-29%
Week 12	A - P	4.41	6.32	-1.91	(-4.74, 0.92)	-30%
	B - P	3.84	6.32	-2.47	(-5.37, 0.43)	-39%
	C - P	4.13	6.32	-2.19	(-4.78, 0.40)	-35%
Change from Day 3-5 to Week 12	A - P	-1.98	-1.99	0.02	(-1.50, 1.53)	-
	B - P	-1.63	-1.99	0.36	(-1.14, 1.86)	-
	C - P	-1.80	-1.99	0.19	(-1.17, 1.55)	-
Left ventricular ejection fraction (LVEF) (%)						
Day 3-5	A - P	56.01	52.13	3.88	(-1.37, 9.12)	7%
	B - P	57.71	52.13	5.57	(0.15, 11.00)	11%
	C - P	56.86	52.13	4.72	(-0.06, 9.51)	9%
Week 12	A - P	59.36	55.14	4.22	(-1.18, 9.62)	8%
	B - P	61.19	55.14	6.05	(0.63, 11.47)	11%
	C - P	60.28	55.14	5.14	(0.28, 10.00)	9%
Change from Day 3-5 to Week 12	A - P	3.35	3.01	0.34	(-3.88, 4.57)	-
	B - P	3.49	3.01	0.48	(-3.67, 4.63)	-
	C - P	3.42	3.01	0.41	(-3.35, 4.17)	-
Left ventricular end-diastolic volume (LVEDV) (mL)						
Day 3-5	A - P	121.45	147.06	-25.61	(-46.27, -4.95)	-17%
	B - P	132.90	147.06	-14.16	(-35.53, 7.20)	-10%
	C - P	127.18	147.06	-19.89	(-38.74, -1.03)	-14%
Week 12	A - P	126.30	147.83	-21.53	(-40.27, -2.79)	-15%
	B - P	129.18	147.83	-18.65	(-37.58, 0.29)	-13%
	C - P	127.74	147.83	-20.09	(-37.01, -3.18)	-14%
Change from Day 3-5 to Week 12	A - P	4.85	0.77	4.08	(-9.55, 17.71)	-
	B - P	-3.72	0.77	-4.49	(-17.95, 8.97)	-
	C - P	0.56	0.77	-0.21	(-12.38, 11.97)	-
Left ventricular end-systolic volume (LVESV) (mL)						
Day 3-5	A - P	54.26	71.65	-17.38	(-31.98, -2.78)	-24%
	B - P	58.00	71.65	-13.64	(-28.74, 1.45)	-19%
	C - P	56.13	71.65	-15.51	(-28.84, -2.19)	-22%
Week 12	A - P	52.17	67.99	-15.82	(-29.51, -2.14)	-23%
	B - P	50.78	67.99	-17.22	(-31.14, -3.29)	-25%
	C - P	51.47	67.99	-16.52	(-28.91, -4.13)	-24%
Change from Day 3-5 to Week 12	A - P	-2.09	-3.65	1.56	(-6.41, 9.52)	-
	B - P	-7.23	-3.65	-3.57	(-11.40, 4.26)	-
	C - P	-4.66	-3.65	-1.01	(-8.11, 6.09)	-

Left ventricular mass (g)						
Day 3-5	A - P	152.17	177.06	-24.89	(-55.07, 5.29)	-14%
	B - P	160.68	177.06	-16.38	(-47.59, 14.82)	-9%
	C - P	156.43	177.06	-20.64	(-48.18, 6.91)	-12%
Week 12	A - P	141.86	164.07	-22.21	(-49.51, 5.09)	-14%
	B - P	156.94	164.07	-7.13	(-35.22, 20.96)	-4%
	C - P	149.40	164.07	-14.67	(-39.52, 10.18)	-9%
Change from Day 3-5 to Week 12	A - P	-10.31	-13.00	2.68	(-6.65, 12.01)	-
	B - P	-3.74	-13.00	9.25	(0.05, 18.46)	-
	C - P	-7.03	-13.00	5.97	(-2.36, 14.30)	-
Wall motion score index						
Day 3-5	A - P	0.25	0.46	-0.20	(-0.40, -0.01)	-43%
	B - P	0.24	0.46	-0.22	(-0.42, -0.01)	-48%
	C - P	0.25	0.46	-0.21	(-0.39, -0.03)	-46%
Week 12	A - P	0.15	0.39	-0.23	(-0.44, -0.03)	-59%
	B - P	0.14	0.39	-0.24	(-0.45, -0.04)	-62%
	C - P	0.15	0.39	-0.24	(-0.42, -0.06)	-62%
Change from Day 3-5 to Week 12	A - P	-0.10	-0.07	-0.03	(-0.15, 0.09)	-
	B - P	-0.10	-0.07	-0.03	(-0.14, 0.09)	-
	C - P	-0.10	-0.07	-0.03	(-0.13, 0.08)	-
Hyperenhancement score index						
Day 3-5	A - P	0.34	0.42	-0.08	(-0.24, 0.08)	-19%
	B - P	0.30	0.42	-0.13	(-0.29, 0.03)	-31%
	C - P	0.32	0.42	-0.10	(-0.25, 0.04)	-24%
Week 12	A - P	0.27	0.38	-0.11	(-0.26, 0.04)	-29%
	B - P	0.22	0.38	-0.17	(-0.32, -0.01)	-45%
	C - P	0.24	0.38	-0.14	(-0.28, -0.00)	-37%
Change from Day 3-5 to Week 12	A - P	-0.08	-0.04	-0.03	(-0.10, 0.03)	-
	B - P	-0.08	-0.04	-0.04	(-0.10, 0.03)	-
	C - P	-0.08	-0.04	-0.04	(-0.09, 0.02)	-

Results from repeated measures of ANCOVA model.

a. Relative change (%) calculated as absolute difference divided by reference (placebo) value x100.

AEs and SAEs (on-therapy and post-therapy) were collected from the start of investigational product.				
		Losmapimod		
	Placebo	7.5 mg BID	Loading dose + 7.5 mg BID	Combined
	n (%)	n (%)	n(%)	n(%)
N (Safety Population)	135	199	192	391
Subjects with any AE [a]	**97 (72)**	**138 (69)**	**131 (68)**	**269 (69)**
10 most frequent AEs in each group				
Chest pain	10 (7)	17 (9)	13 (7)	30 (8)
Headache	9 (7)	15 (8)	12 (6)	27 (7)
Dizziness	12 (9)	11 (6)	7 (4)	18 (5)
Haematoma	8 (6)	11 (6)	6 (3)	17 (4)
Constipation	4 (3)	7 (4)	8 (4)	15 (4)
Anaemia	3 (2)	7 (4)	5 (3)	12 (3)
Angina pectoris	6 (4)	7 (4)	5 (3)	12 (3)
Atrial fibrillation	8 (6)	4 (2)	7 (4)	11 (3)
Nausea	8 (6)	7 (4)	4 (2)	11 (3)
Hypotension	5 (4)	5 (3)	6 (3)	11 (3)
Rash	3 (2)	7 (4)	4 (2)	11 (3)
Diarrhoea	7 (5)	4 (2)	6 (3)	10 (3)
Dyspnoea	7 (5)	6 (3)	4 (2)	10 (3)
Nasopharyngitis	7 (5)	1 (<1)	9 (5)	10 (3)
Acute myocardial infarction	2 (1)	4 (2)	6 (3)	10 (3)
Fatigue	10 (7)	4 (2)	5 (3)	9 (2)
Anxiety	2 (1)	7 (4)	1 (<1)	8 (2)
Myocardial infarction	7 (5)	4 (2)	1 (<1)	5 (1)
a. This table includes on-therapy and post-therapy AEs.				

Serious Adverse Events **n (%) [n considered by the investigator to be related to study medication]**				
	Placebo	**7.5 mg BID**	**Loading dose + 7.5 mg BID**	**Combined**
	N=135	**N=199**	**N=192**	**N=391**
	n (%) [related]	**n (%) [related]**	**n (%) [related]**	**n (%) [related]**
N (Safety Population)	135	199	192	391
Subjects with any fatal or non-fatal SAE [a, b]	**32 (24) [3]**	**51 (26) [9]**	**43 (22) [0]**	**94 (24) [9]**
Acute myocardial infarction	2 (1) [1]	4 (2) [1]	6 (3) [0]	10 (3) [1]
Angina unstable	3 (2) [0]	4 (2) [0]	5 (3) [0]	9 (2) [0]
Chest pain	3 (2) [1]	4 (2) [0]	4 (2) [0]	8 (2) [0]
Cardiac failure	0	2 (1) [0]	4 (2) [0]	6 (2) [0]
Atrial fibrillation	1 (<1) [0]	2 (1) [0]	3 (2) [0]	5 (1) [0]
Myocardial infarction	7 (5) [0]	4 (2) [0]	1 (<1) [0]	5 (1) [0]
Angina pectoris	4 (3) [0]	1 (<1) [1]	3 (2) [0]	4 (1) [1]
Cardiogenic shock	1 (<1) [0]	2 (1) [0]	2 (1) [0]	4 (1) [0]
Cardiac failure congestive	0	2 (1) [0]	1 (<1) [0]	3 (<1) [0]
Cerebrovascular accident	0	1 (<1) [0]	2 (1) [0]	3 (<1) [0]
Pleural effusion	0	2 (1) [0]	1 (<1) [0]	3 (<1) [0]
Pulmonary embolism	0	2 (1) [1]	1 (<1) [0]	3 (<1) [1]
Renal failure	0	3 (2) [1]	0	3 (<1) [1]
Respiratory failure	0	3 (2) [0]	0	3 (<1) [0]
Vascular pseudoaneurysm	0	1 (<1) [0]	2 (1) [0]	3 (<1) [0]
Acute pulmonary oedema	0	2 (1) [0]	0	2 (<1) [0]

Anaemia	0	1 (<1) [0]	1 (<1) [0]	2 (<1) [0]
Arrhythmia	1 (<1) [0]	0	2 (1) [0]	2 (<1) [0]
Coronary artery disease	0	0	2 (1) [0]	2 (<1) [0]
Non-cardiac chest pain	1 (<1) [0]	0	2 (1) [0]	2 (<1) [0]
Pneumonia	0	2 (1) [0]	0	2 (<1) [0]
Post procedural myocardial infarction	0	1 (<1) [0]	1 (<1) [0]	2 (<1) [0]
Pulmonary oedema	0	1 (<1) [0]	1 (<1) [0]	2 (<1) [0]
Thrombosis in device	2 (1) [2]	0	1 (<1) [0]	1 (<1) [0]
Cardiac arrest	1 (<1) [0]	1 (<1) [0]	0	1 (<1) [0]
Epistaxis	1 (<1) [0]	0	1 (<1) [0]	1 (<1) [0]
Gastrointestinal haemorrhage	1 (<1) [0]	1 (<1) [1]	0	1 (<1) [1]
Ischaemic stroke	1 (<1) [0]	1 (<1) [0]	0	1 (<1) [0]
Multi-organ failure	1 (<1) [0]	0	1 (<1) [0]	1 (<1) [0]
Syncope	1 (<1) [0]	1 (<1) [0]	0	1 (<1) [0]
Ventricular fibrillation	1 (<1) [0]	1 (<1) [0]	0	1 (<1) [0]
Wound dehiscence	1 (<1) [0]	0	1 (<1) [0]	1 (<1) [0]
Abdominal adhesions	0	0	1 (<1) [0]	1 (<1) [0]
Abdominal pain	1 (<1) [0]	0	0	0
Abdominal pain upper	0	0	1 (<1) [0]	1 (<1) [0]
Acute coronary syndrome	0	0	1 (<1) [0]	1 (<1) [0]
Acute respiratory failure	0	1 (<1) [1]	0	1 (<1) [1]
Anxiety	0	1 (<1) [0]	0	1 (<1) [0]
Arterial haemorrhage	0	1 (<1) [0]	0	1 (<1) [0]
Arterial thrombosis limb	0	1 (<1) [0]	0	1 (<1) [0]
Atrioventricular block complete	0	1 (<1) [0]	0	1 (<1) [0]
Cardiac tamponade	0	0	1 (<1) [0]	1 (<1) [0]
Cardio-respiratory arrest	0	0	1 (<1) [0]	1 (<1) [0]
Cellulitis	0	0	1 (<1) [0]	1 (<1) [0]
Cerebral haemorrhage	0	0	1 (<1) [0]	1 (<1) [0]
Cerebral infarction	0	0	1 (<1) [0]	1 (<1) [0]
Cervical vertebral fracture	0	0	1 (<1) [0]	1 (<1) [0]
Cholelithiasis	0	1 (<1) [0]	0	1 (<1) [0]
Coronary artery occlusion	0	1 (<1) [0]	0	1 (<1) [0]
Cough	0	1 (<1) [0]	0	1 (<1) [0]
Death	0	1 (<1) [0]	0	1 (<1) [0]
Deep vein thrombosis	0	0	1 (<1) [0]	1 (<1) [0]
Delusion	0	0	1 (<1) [0]	1 (<1) [0]
Dementia	0	1 (<1) [0]	0	1 (<1) [0]
Dressler's syndrome	0	1 (<1) [0]	0	1 (<1) [0]
Duodenal ulcer perforation	0	1 (<1) [1]	0	1 (<1) [1]
Dyspnoea	0	1 (<1) [0]	0	1 (<1) [0]
Eczema	0	1 (<1) [0]	0	1 (<1) [0]
Encephalopathy	0	1 (<1) [0]	0	1 (<1) [0]
Epilepsy	0	1 (<1) [1]	0	1 (<1) [1]
Extrasystoles	0	0	1 (<1) [0]	1 (<1) [0]
Gastric cancer	0	0	1 (<1) [0]	1 (<1) [0]
Gastric ulcer	0	1 (<1) [0]	0	1 (<1) [0]
Gastroenteritis norovirus	0	1 (<1) [0]	0	1 (<1) [0]
Haemorrhage intracranial	0	1 (<1) [0]	0	1 (<1) [0]
Headache	0	0	1 (<1) [0]	1 (<1) [0]
Hepatic function abnormal	0	1 (<1) [1]	0	1 (<1) [1]
Hypertensive crisis	0	1 (<1) [0]	0	1 (<1) [0]
Hypokalaemia	0	1 (<1) [0]	0	1 (<1) [0]
Hypoxic-ischaemic encephalopathy	0	1 (<1) [0]	0	1 (<1) [0]
Ileus	0	0	1 (<1) [0]	1 (<1) [0]

In-stent coronary artery restenosis	0	1 (<1) [0]	0	1 (<1) [0]
Intracardiac thrombus	0	0	1 (<1) [0]	1 (<1) [0]
Ischaemic hepatitis	0	1 (<1) [0]	0	1 (<1) [0]
Loss of consciousness	0	1 (<1) [0]	0	1 (<1) [0]
Mental status changes	0	1 (<1) [0]	0	1 (<1) [0]
Musculoskeletal chest pain	0	0	1 (<1) [0]	1 (<1) [0]
Myeloproliferative disorder	0	0	1 (<1) [0]	1 (<1) [0]
Orthostatic hypotension	0	0	1 (<1) [0]	1 (<1) [0]
Peripheral vascular disorder	0	0	1 (<1) [0]	1 (<1) [0]
Phlebitis	0	1 (<1) [0]	0	1 (<1) [0]
Postoperative thoracic procedure complication	0	1 (<1) [0]	0	1 (<1) [0]
Postoperative wound complication	0	1 (<1) [0]	0	1 (<1) [0]
Procedural complication	0	0	1 (<1) [0]	1 (<1) [0]
Rash	0	1 (<1) [1]	0	1 (<1) [1]
Rectal neoplasm	0	1 (<1) [0]	0	1 (<1) [0]
Renal colic	0	0	1 (<1) [0]	1 (<1) [0]
Respiratory arrest	0	1 (<1) [0]	0	1 (<1) [0]
Right ventricular failure	0	0	1 (<1) [0]	1 (<1) [0]
Shock haemorrhagic	0	0	1 (<1) [0]	1 (<1) [0]
Streptococcal sepsis	0	1 (<1) [0]	0	1 (<1) [0]
Subclavian artery stenosis	0	1 (<1) [0]	0	1 (<1) [0]
Supraventricular tachycardia	0	1 (<1) [0]	0	1 (<1) [0]
Tachyarrhythmia	0	1 (<1) [0]	0	1 (<1) [0]
Transient ischaemic attack	0	1 (<1) [0]	0	1 (<1) [0]
Upper gastrointestinal haemorrhage	0	1 (<1) [0]	0	1 (<1) [0]
Urosepsis	0	1 (<1) [0]	0	1 (<1) [0]
Ventricular asystole	0	1 (<1) [0]	0	1 (<1) [0]
Ventricular dysfunction	0	1 (<1) [0]	0	1 (<1) [0]
Wound infection staphylococcal	0	1 (<1) [1]	0	1 (<1) [1]
Dizziness	2 (1) [0]	0	0	0
Convulsion	1 (<1) [1]	0	0	0
Hypertension	1 (<1) [0]	0	0	0
Labyrinthitis	1 (<1) [0]	0	0	0
Presyncope	1 (<1) [0]	0	0	0
Prostate cancer	1 (<1) [0]	0	0	0
Renal failure acute	1 (<1) [0]	0	0	0
Upper limb fracture	1 (<1) [0]	0	0	0
Ventricular tachycardia	1 (<1) [0]	0	0	0

a. This table includes on-therapy and post-therapy SAEs.
b. There were no fatal SAEs considered by the investigator to be related to study medication.

The frequency of liver events (i.e. alanine aminotransferase [ALT] ≥3x upper limit of normal [ULN] as measured by the central laboratory and/or investigator-recorded significant liver event with associated local laboratory ALT ≥3xULN) was 0.7% (1/135 subjects) for the placebo group and 2.0% (8/391 subjects) for the combined losmapimod group. There were no Hy's rule events (i.e. ALT ≥3x ULN and bilirubin ≥2x ULN simultaneously without other identified causes).

At Week 12 an increase of 7% in serum creatinine (ratio 1.07 [95% CI: 1.02, 1.11]), and a corresponding increase in BUN (ratio 1.07 [95% CI: 1.00, 1.14]) and decrease in calculated GFR (ratio 0.94, [95% CI: 0.90, 0.98]), were observed for the combined losmapimod group versus placebo, which attenuated during follow-up. The proportion of subjects with a 2-fold increase in serum creatinine over baseline was 3% (3/115 subjects) in the placebo group and 2% (7/324 subjects) in the combined losmapimod group.

There were no differences between placebo and losmapimod groups with regard to other laboratory safety tests, vital signs or ECGs.

Conclusions:

There was no statistically significant difference in hsCRP at Week 12 between the combined losmapimod and placebo groups. There was no statistically significant difference in average cTnI concentration during the in-hospital period between the combined losmapimod and placebo groups. The incidences of AEs and SAEs were similar between the combined losmapimod and placebo groups. There were no statistically significant reductions in MACE for the total study for the combined losmapimod group compared with placebo. The incidence of mortality was similar between the combined losmapimod and placebo groups.