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**: PM1111138

**Title :** A double-blind, placebo-controlled, parallel group study to evaluate the effects of two regimens of losmapimod (GW856553), over a period of 3 months, on in vivo macrophage activity, as assessed by FDG-PET/CT imaging, in the carotid arteries and aorta of subjects with established atherosclerosis

**Rationale:** Atherosclerosis is a chronic progressive inflammatory disease. The p38 mitogen-activated protein kinase (MAPK) cascade appears to play a key role in the initiation and progression of inflammatory diseases. Losmapimod is an inhibitor of p38α MAPK and is being developed for a variety of inflammatory conditions, including atherosclerosis. Losmapimod is likely to be co-administered with lipid lowering therapy, so this study was conducted in subjects who were already on stable statin therapy, in order to establish whether losmapimod exhibited a benefit additive to that of statins. Fluorodeoxyglucose (FDG) positron emission tomography (PET)/computed tomography (CT) imaging was used in order to assess the potential anti-inflammatory effects of treatment with losmapimod for 12 weeks on inflammatory activity within aortic and carotid plaques.

**Phase:** II

**Study Period:** 02 June 2008 to 03 December 2009

**Study Design:** Randomized, repeat-dose, double-blind, placebo-controlled, parallel-group (3 arms)

**Centres:** 4 centres in the United Kingdom.

**Indication:** Atherosclerosis

**Treatment:** Oral dosing for 12 weeks (84 days) with:

- Losmapimod 7.5 mg twice daily (BID) (morning and evening doses) (group A)
- Losmapimod 7.5 mg once daily (QD) (morning dose) and placebo (evening dose) (group B).
- Placebo (morning and evening doses) (group P).

**Objectives:**

**Primary objective**:

- To measure in-vivo macrophage activity, by FDG-PET/CT imaging, in carotid arteries and aorta following 12 weeks treatment with losmapimod (7.5 mg QD or 7.5 mg BID), in the setting of chronic statin therapy, as compared to placebo.

**Secondary objectives**:

- To evaluate the safety and tolerability of 12 weeks of dosing with losmapimod (7.5 mg QD and 7.5 mg BID).
- To evaluate the effect of 12 weeks of dosing with losmapimod on inflammatory biomarkers.
- To determine the effect of short-term p38 MAPK inhibition (once daily dosing of 7.5 mg losmapimod) versus the effect of 24 hour p38 MAPK inhibition (twice daily dosing of 7.5 mg losmapimod), over a period of 12 weeks, on in-vivo macrophage activity, as assessed by FDG-PET/CT imaging, in the setting of chronic statin therapy.

**Statistical Methods:** A sufficient number of subjects was enrolled so that approximately 90 subjects (30 subjects per arm) completed the study. Sample size was based in part on feasibility. Change from baseline tissue to background ratio (TBR) and percent change from baseline TBR were analyzed using analysis of covariance (ANCOVA), fitting fixed effect treatment term, and including baseline TBR value as a covariate. Point estimates and corresponding 95% confidence intervals (CIs) were constructed for the relevant comparisons of interest (A-P, B-P, A-B). From the same model, the Least Squares (LS) mean of each treatment and the corresponding 95% CI were derived for the change from baseline for each treatment. The proportion of active slices was analyzed using a logistic regression model, fitting terms for treatment and including the baseline proportion of active slices as covariate. Point estimates and corresponding 95% CIs were constructed to establish the odds ratio for the relevant comparisons of interest (A-P, B-P).

Biomarker data were analyzed by ANCOVA fitting terms for regimen, day and interaction of day and regimen as fixed effects, subject as a random effect, and baseline biomarker at Day 1 as a covariate. The comparisons of losmapimod BID versus placebo and losmapimod QD versus placebo on Day 42 and Day 84 were obtained. Point estimates and corresponding 95% CIs for the difference of interest for A - P (or A/P, if data were loge-transformed), and B - P (or B/P, if data were $\log_e$-transformed) were constructed using the residual variance.

- Safety population: All subjects who received at least one dose of investigational product. Subjects were classified according to the treatment received.
- Pharmacodynamic population: Subjects who provided any pharmacodynamic data (i.e., FDG-PET or biomarker data). For change from baseline assessments, only those subjects providing both evaluable baseline and post-dose values were included in the analysis.

- Pharmacokinetic concentration population: All subjects from whom a pharmacokinetic (PK) sample was obtained and analyzed.

**Study Population:** Male and female subjects between 50 and 80 years of age, inclusive, with a body weight >50 kg and body mass index between 19 and 35 kg/m$^2$ who had:

- experienced a cardiovascular event (ie, acute coronary syndrome, unstable angina coronary artery bypass graft, percutaneous coronary intervention, stroke, myocardial infarction, transient ischaemic attack, carotid endarterectomy), but had been clinically stable for at least 6 months since that event;
- or, had peripheral vascular disease as indicated by symptoms of claudication and a positive imaging/treadmill test, or reduced ankle-brachial pressure index;
- or, had a diagnosis of coronary artery disease corroborated by stress testing (exercise or pharmacological) or any other confirmed diagnosis of atherosclerotic arterial disease.

Subjects had to be on a stable dose of statin for at least 3 months prior to first dose of investigational product and to be capable of continuing statin therapy from screening until the final follow-up visit. Subjects had to have either carotid or aortic TBR ≥1.6, as measured on FDG-PET/CT, signifying active inflammation, and aspartate aminotransferase and alanine aminotransferase <2x upper limit of normal (ULN) at screening and alkaline phosphatase and bilirubin ≤1.5x ULN at screening (isolated bilirubin >1.5xULN was acceptable if bilirubin was fractionated and direct bilirubin <35%).

| Number of Subjects | Losmapimod 7.5 mg BID | Losmapimod 7.5 mg QD | Placebo | Total |
|---|---|---|---|---|
| Planned, N | 30 | 30 | 30 | 90 |
| Dosed, N | 34 | 33 | 32 | 99 |
| Completed, n (%) | 33 (97) | 32 (97) | 27 (84) | 92 (93) |
| Total number subjects withdrawn, n (%) | 1 (3) | 1 (3) | 5 (16) | 7 (7) |
| Withdrawn due to adverse events, n (%) | 1 (3) | 0 | 5 (16) | 6 (6) |
| Withdrawn due to lack of efficacy, n (%) | 0 | 0 | 0 | 0 |
| Withdrawn for other reasons, n (%) | 0 | 1 (3) | 0 (0) | 1 (1) |
| **Demographics** | **Losmapimod 7.5 mg BID** | **Losmapimod 7.5 mg QD** | **Placebo** | **Total** |
| N (Safety population) | 34 | 33 | 32 | 99 |
| Females: Males | 5 : 29 | 5 : 28 | 4 : 28 | 14 : 85 |
| Mean age in years (sd) | 62.3 (5.90) | 65.3 (5.94) | 63.7 (6.37) | 63.8 (6.13) |
| Mean weight in kg (sd) | 89.6 (11.90) | 82.3 (12.59) | 87.5 (12.76) | 86.5 (12.68) |
| White, n (%) | 32 (94) | 30 (91) | 30 (94) | 92 (93) |
| Asian, n (%) | 1 (3) | 1 (3) | 1 (3) | 3 (3) |
| African American/African Heritage, n (%) | 1 (3) | 2 (6) | 1 (3) | 4 (4) |

**Pharmacodynamic Results:**

**Comparison of change from baseline for mean of maximum TBR for qualifying artery (primary endpoint)**

| | Qualifying artery TBR, mean (SD) | | Day 84 versus baseline | | | Placebo and baseline corrected | | |
|---|---|---|---|---|---|---|---|---|
| Group | Baseline | Day 84 | Diff | 95% CI | P-value | Diff | 95% CI | P-value |
| A (n=34) | 2.07 (0.311) | 1.93 (0.302) | -0.13 | -0.21, -0.05 | 0.0025 | -0.04 | -0.14, 0.06 | 0.4519 |
| B (n=33) | 2.05 (0.223) | 1.93 (0.202) | -0.12 | -0.17, -0.06 | 0.0003 | -0.02 | -0.11, 0.06 | 0.5789 |
| P (n=32) | 1.94 (0.242) | 1.89 (0.249) | -0.09 | -0.16, -0.03 | 0.0052 | - | - | - |

A = losmapimod 7.5 mg BID; B = losmapimod 7.5 mg QD; P = placebo.

**Comparison of change from baseline for mean of maximum TBR for most diseased segment (MDS) of qualifying artery (secondary endpoint)**

| | MDS TBR, mean (SD) | | Day 84 versus baseline | | | Placebo and baseline corrected | | |
|---|---|---|---|---|---|---|---|---|
| Group | Baseline | Day 84 | Diff | 95% CI | P-value | Diff | 95% CI | P-value |
| A (n=34) | 2.33 (0.469) | 2.06 (0.389) | -0.27 | -0.37, -0.17 | <0.0001 | -0.02 | -0.15 ,0.10 | 0.6986 |
| B (n=33) | 2.28 (0.299) | 2.03 (0.318) | -0.25 | -0.35, -0.15 | <0.0001 | -0.00 | -0.13, 0.12 | 0.9486 |
| P (n=32) | 2.20 (0.279) | 1.99 (0.298) | -0.25 | -0.33, -0.17 | <0.0001 | - | - | - |

A = losmapimod 7.5 mg BID; B = losmapimod 7.5 mg QD; P = placebo.

**Comparison of change from baseline for mean of maximum TBR for active segments* of qualifying artery (exploratory endpoint)**

| | Active segments TBR, mean (SD) | | Day 84 versus baseline | | | Placebo and baseline corrected | | |
|---|---|---|---|---|---|---|---|---|
| Group | Baseline | Day 84 | Diff | 95% CI | P-value | Diff | 95% CI | P-value |
| A (n=34) | 2.03 (0.30) | 1.86 (0.27) | -0.14 | -0.20, -0.08 | <0.0001 | -0.10 | -0.19, -0.02 | 0.0125 |
| B (n=33) | 2.03 (0.22) | 1.87 (0.19) | -0.14 | -0.20, -0.07 | <0.0001 | -0.10 | -0.18, -0.02 | 0.0194 |
| P (n=32) | 1.86 (0.20) | 1.84 (0.20) | -0.04 | -0.09, 0.02 | 0.1773 | - | - | - |

A = losmapimod 7.5 mg BID; B = losmapimod 7.5 mg QD; P = placebo.

* Active segments defined as slices with maximum TBR ≥1.6.

**Comparison of change from baseline in length of active segments* in the qualifying artery (exploratory endpoint)**

| | Length of active segments, geometric mean (95% CI) | | Day 84 versus baseline | | | Placebo and baseline corrected | | |
|---|---|---|---|---|---|---|---|---|
| Group | Baseline | Day 84 | Ratio | 95% CI | p-value | Ratio | 95% CI | p-value |
| A (n=34) | 7.8 (5.8, 10.4) | 4.4 (3.3, 5.9) | 0.56 | 0.38, 0.83 | 0.0036 | 0.56 | 0.33, 0.95 | 0.030* |
| B (n=33) | 9.9 (7.5, 13.1) | 5.7 (4.1, 7.9) | 0.59 | 0.40, 0.88 | 0.0098 | 0.59 | 0.35, 1.00 | 0.0507 |
| P (n=32) | 4.7 (3.6, 6.1) | 5.2 (3.8, 6.9) | 1.00 | 0.71, 1.42 | 0.9898 | - | - | - |

A = losmapimod 7.5 mg BID; B = losmapimod 7.5 mg QD; P = placebo.

* Active segments defined as slices with maximum TBR ≥1.6.

**Comparison of change from baseline in the proportion of active slices with TBR ≥1.6 in the qualifying artery (exploratory endpoint)**

| | Proportion of active slices, % (SD) | | Day 84 versus baseline | | | Placebo and baseline corrected | | |
|---|---|---|---|---|---|---|---|---|
| Group | Baseline | Day 84 | Odds ratio | 95% CI | P-value | Odds ratio | 95% CI | P-value |
| A (n=34) | 94.4 (9.4) | 84.6 (21.3) | 0.19 | 0.08, 0.47 | 0.0002 | 0.57 | 0.41, 0.81 | 0.0016 |
| B (n=33) | 95.3 (8.2) | 89.1 (19.7) | 0.39 | 0.22, 0.69 | 0.0012 | 1.17 | 0.80, 1.71 | 0.4287 |
| P (n=32) | 88.3 (19.2) | 82.2 (24.4) | 0.90 | 0.50, 1.62 | 0.7358 | - | - | - |

A = losmapimod 7.5 mg BID; B = losmapimod 7.5 mg QD; P = placebo.

**Comparison of change from baseline for maximum standard uptake value (SUV) for subcutaneous and visceral fat (exploratory endpoint)**

| | SUV for subcutaneous fat, Mean (SD) | | Day 84 versus baseline | | | Placebo and baseline corrected | | |
|---|---|---|---|---|---|---|---|---|
| Group | Baseline | Day 84 | Diff | 95% CI | P-value | Diff | 95% CI | P-value |
| A (n=34) | 0.32 (0.085) | 0.30 (0.095) | -0.02 | -0.05, 0.00 | 0.0602 | -0.00 | -0.04, 0.03 | 0.8150 |
| B (n=33) | 0.34 (0.084) | 0.31 (0.079) | -0.03 | -0.05, -0.00 | 0.0199 | -0.01 | -0.05, 0.03 | 0.6355 |
| P (n=32) | 0.34 (0.112) | 0.32 (0.108) | -0.02 | -0.05, 0.01 | 0.1684 | - | - | - |
| | SUV for visceral fat, Mean (SD) | | Day 84 versus baseline | | | Placebo and baseline corrected | | |
| Group | Baseline | Day 84 | Diff | 95% CI | P-value | Diff | 95% CI | P-value |
| A (n=34) | 0.59 (0.110) | 0.53 (0.120) | -0.06 | -0.09, -0.02 | 0.0015 | -0.05 | -0.09, -0.01 | 0.0177 |
| B (n=33) | 0.58 (0.133) | 0.56 (0.140) | -0.02 | -0.06, 0.02 | 0.2744 | -0.02 | -0.06, 0.03 | 0.5022 |
| P (n=32) | 0.57 (0.130) | 0.57 (0.081) | -0.01 | -0.03, 0.02 | 0.6537 | - | - | - |

A = losmapimod 7.5 mg BID; B = losmapimod 7.5 mg QD; P = placebo.

| Baseline corrected comparison of ratio of high sensitivity C-reactive protein (hsCRP) (secondary endpoint) | | | | |
|---|---|---|---|---|
| **Parameter** | **Comparison** | **Ratio** | **95% CI** | **P-value** |
| Baseline corrected comparison of hsCRP between losmapimod 7.5 mg BID and placebo | A (Day 7 : Day 1) : P (Day 7 : Day 1) | 0.41 | 0.26, 0.64 | 0.0001 |
| | A (Day 14 : Day 1) : P (Day 14 : Day 1) | 0.72 | 0.50, 1.02 | 0.0645 |
| | A (Day 28 : Day 1) : P (Day 28 : Day 1) | 0.73 | 0.51, 1.03 | 0.0758 |
| | A (Day 56 : Day 1) : P (Day 56 : Day 1) | 0.69 | 0.48, 1.00 | 0.0503 |
| | A (Day 84 : Day 1) : P (Day 84 : Day 1) | 0.78 | 0.54, 1.13 | 0.1873 |
| | A (average : Day 1) : P (average : Day 1) | 0.72 | 0.54, 0.95 | 0.0230 |
| | A (FU : Day 1) : P (FU : Day 1) | 1.47 | 1.03, 2.10 | 0.0346 |
| Baseline corrected comparison of hsCRP between losmapimod 7.5 mg QD and placebo | B (Day 7 : Day 1) : P (Day 7 : Day 1) | 0.57 | 0.35, 0.91 | 0.0178 |
| | B (Day 14 : Day 1) : P (Day 14 : Day 1) | 0.70 | 0.49, 0.99 | 0.0448 |
| | B (Day 28 : Day 1) : P (Day 28 : Day 1) | 0.78 | 0.55, 1.12 | 0.1848 |
| | B (Day 56 : Day 1) : P (Day 56 : Day 1) | 0.64 | 0.44, 0.92 | 0.0165 |
| | B (Day 84 : Day 1) : P (Day 84 : Day 1) | 0.93 | 0.64, 1.36 | 0.7164 |
| | B (average : Day 1) : P (average : Day 1) | 0.80 | 0.60, 1.06 | 0.1202 |
| | B (FU : Day 1) : P (FU : Day 1) | 1.28 | 0.89, 1.83 | 0.1828 |
| A = losmapimod 7.5 mg BID; B = losmapimod 7.5 mg QD; P = placebo. | | | | |

| Baseline corrected comparison of ratio of plasma biomarkers for losmapimod 7.5 mg BID group compared with placebo* (secondary endpoint) | | | | |
|---|---|---|---|---|
| **Parameter** | **Comparison** | **Ratio** | **95% CI** | **P-value** |
| Homocysteine | A (day 28 : day 1) : P (day 28 : day 1) | 0.99 | 0.87, 1.12 | 0.8305 |
| | A (day 84 : day 1) : P (day 84 : day 1) | 0.87 | 0.76, 0.99 | 0.0368 |
| intercellular adhesion molecule 1 | A (day 28 : day 1) : P (day 28 : day 1) | 1.03 | 0.81, 1.30 | 0.8181 |
| | A (day 84 : day 1) : P (day 84 : day 1) | 0.97 | 0.76, 1.23 | 0.7923 |
| Interleukin-18 | A (day 28 : day 1) : P (day 28 : day 1) | 0.97 | 0.85, 1.12 | 0.6999 |
| | A (day 84 : day 1) : P (day 84 : day 1) | 1.00 | 0.87, 1.15 | 0.9549 |
| Interleukin-6 | A (day 28 : day 1) : P (day 28 : day 1) | 0.97 | 0.58, 1.61 | 0.9015 |
| | A (day 84 : day 1) : P (day 84 : day 1) | 0.85 | 0.51, 1.42 | 0.5263 |
| Interleukin-8 | A (day 28 : day 1) : P (day 28 : day 1) | 0.90 | 0.70, 1.15 | 0.4020 |
| | A (day 84 : day 1) : P (day 84 : day 1) | 0.73 | 0.57, 0.94 | 0.0151 |
| Monocyte chemotactic protein 1 | A (day 28 : day 1) : P (day 28 : day 1) | 0.95 | 0.82, 1.10 | 0.4747 |
| | A (day 84 : day 1) : P (day 84 : day 1) | 0.81 | 0.70, 0.95 | 0.0072 |
| Matrix metalloproteinase (MMP) 2 | A (day 28 : day 1) : P (day 28 : day 1) | 1.03 | 0.93, 1.14 | 0.5864 |
| | A (day 84 : day 1) : P (day 84 : day 1) | 1.02 | 0.91, 1.13 | 0.7654 |
| MMP9E | A (day 28 : day 1) : P (day 28 : day 1) | 0.72 | 0.54, 0.96 | 0.0252 |
| | A (day 84 : day 1) : P (day 84 : day 1) | 0.75 | 0.56, 1.01 | 0.0601 |
| MMP9-neutrophil gelatinase - associated lipocalin | A (day 28 : day 1) : P (day 28 : day 1) | 0.68 | 0.48, 0.95 | 0.0235 |
| | A (day 84 : day 1) : P (day 84 : day 1) | 0.66 | 0.47, 0.94 | 0.0200 |
| Neopterin | A (day 28 : day 1) : P (day 28 : day 1) | 0.99 | 0.90, 1.10 | 0.9098 |
| | A (day 84 : day 1) : P (day 84 : day 1) | 1.04 | 0.93, 1.15 | 0.5074 |
| Osteopontin | A (day 28 : day 1) : P (day 28 : day 1) | 0.96 | 0.80, 1.16 | 0.7006 |
| | A (day 84 : day 1) : P (day 84 : day 1) | 0.90 | 0.75, 1.09 | 0.2775 |
| Tissue factor | A (day 28 : day 1) : P (day 28 : day 1) | 0.79 | 0.64, 0.99 | 0.0403 |
| | A (day 84 : day 1) : P (day 84 : day 1) | 0.88 | 0.70, 1.10 | 0.2610 |
| Transforming growth factor | A (day 28 : day 1) : P (day 28 : day 1) | 1.12 | 0.88, 1.41 | 0.3567 |
| | A (day 84 : day 1) : P (day 84 : day 1) | 0.89 | 0.70, 1.13 | 0.3283 |
| Von Willebrand factor | A (day 28 : day 1) : P (day 28 : day 1) | 0.98 | 0.86, 1.11 | 0.7172 |
| | A (day 84 : day 1) : P (day 84 : day 1) | 1.00 | 0.88, 1.15 | 0.9557 |
| A = losmapimod 7.5 mg BID; B = losmapimod 7.5 mg QD; P = placebo.<br>* None of the comparisons for the losmapimod 7.5 mg QD group versus placebo were statistically significant. | | | | |

| **Pharmacokinetics Results:** | | | | |
|---|---|---|---|---|
| **Plasma losmapimod pharmacokinetic concentration-time data (ng/mL)** | | | | |
| | **Losmapimod 7.5 mg BID N=32** | | **Losmapimod 7.5 mg QD N=30** | |
| | **n** | **Mean (95% CI)** | **n** | **Mean (95% CI)** |
| Day 28 pre-dose | 20 | 15.4 (10.80, 20.07) | 20 | 3.9 (1.68, 6.20) |
| Day 42 pre-dose | 11 | 12.2 (5.28, 19.17) | 10 | 3.0 (1.93, 4.14) |
| Day 84 pre-dose | 31 | 14.0 (10.59, 17.48) | 30 | 4.9 (2.75, 7.01) |

**Safety results:**
Adverse events (AEs) and serious adverse events (SAEs) were collected and recorded starting on Day 1 and continuing until the end of the study.

| | **Losmapimod 7.5 mg BID** | **Losmapimod 7.5 mg QD** | **Placebo** |
|---|---|---|---|
| N (safety Population) | 34 | 33 | 32 |
| **Subjects with AEs, n (%)** | **29 (85)** | **28 (85)** | **31 (97)** |
| Most frequent adverse events (≥3 subjects in any group) | | | |
| Headache | 7 (21) | 10 (30) | 10 (31) |
| Diarrhoea | 8 (24) | 3 (9) | 3 (9) |
| Fatigue | 4 (12) | 2 (6) | 5 (16) |
| Nasopharyngitis | 5 (15) | 4 (12) | 2 (6) |
| Dizziness | 2 (6) | 3 (9) | 4 (13) |
| Chest pain | 4 (12) | 2 (6) | 2 (6) |
| Arthralgia | 3 (9) | 1 (3) | 3 (9) |
| Cough | 3 (9) | 3 (9) | 1 (3) |
| Muscle spasms | 1 (3) | 3 (9) | 3 (9) |
| Nausea | 3 (9) | 2 (6) | 2 (6) |
| Pain in extremity | 4 (12) | 2 (6) | 1 (3) |
| Back pain | 1 (3) | 0 | 5 (16) |
| Constipation | 3 (9) | 0 | 3 (9) |
| Oropharyngeal pain | 2 (6) | 3 (9) | 1 (3) |
| Palpitations | 2 (6) | 3 (9) | 1 (3) |
| Lung neoplasm | 1 (3) | 1 (3) | 3 (9) |
| C-reactive protein increased | 1 (3) | 3 (9) | 0 |
| Dyspepsia | 3 (9) | 0 | 1 (3) |
| Lethargy | 0 | 0 | 4 (13) |
| Toothache | 4 (12) | 0 | 0 |
| Epistaxis | 0 | 3 (9) | 0 |
| Eye pain | 0 | 3 (9) | 0 |

| **Serious Adverse Events, n (%) [n(%) considered by the investigator to be related, possibly related, or probably related to study medication]** | | | |
|---|---|---|---|
| | **Losmapimod 7.5 mg BID** | **Losmapimod 7.5 mg QD** | **Placebo** |
| N (safety Population) | 34 | 33 | 32 |
| **Subjects with fatal SAEs, n (%) [n (%)]** | **0** | **0** | **1 (3) [0 (0)]** |
| Road traffic accident* | 0 | 0 | 1 (3) [0 (0)] |
| **Subjects with non-fatal SAEs, n (%) [n (%)]** | **4 (12) [1 (3)]** | **1 (3) [0 (0)]** | **2 (6) [2 (6)]** |
| Presyncope | 1 (3) [0 (0)] | 0 | 1 (3) [1 (3)] |
| Chest pain | 1 (3) [0 (0)] | 0 | 0 |
| Costochondritis | 1 (3) [0 (0)] | 0 | 0 |
| Meningitis herpes | 1 (3) [1 (3)] | 0 | 0 |
| Pain | 1 (3) [0 (0)] | 0 | 0 |
| Dizziness | 0 | 1 (3) [0 (0)] | 0 |
| Hyperhidrosis | 0 | 1 (3) [0 (0)] | 0 |
| Vomiting | 0 | 1 (3) [0 (0)] | 0 |
| Bundle branch block left | 0 | 0 | 1 (3) [1 (3)] |
| * Left ventricular failure was identified during autopsy and, in the pathologist's opinion, the cause of death was natural. | | | |

**Conclusion:**

- The primary analysis of change from baseline to Day 84 in FDG uptake (mean of maximum TBR) in the qualifying artery was not statistically significant different between losmapimod 7.5 mg BID compared with placebo (difference -0.04 [95% CI: -0.14, 0.06], p=0.4519), or losmapimod 7.5 mg QD compared with placebo (difference -0.02 [95% CI: -0.11, 0.06], p=0.5789).
- None of the secondary analyses of vascular imaging data showed statistically significant differences among treatment groups for FDG uptake.
- Post-hoc exploratory analyses focusing on the more active parts of the qualifying artery showed that, after adjusting for differences in baseline values, the proportion of active slices (TBR ≥1.6) in the qualifying vessel was significantly reduced from baseline in the BID group compared with placebo (odds ratio 0.57 [95% CI: 0.41, 0.81], p=0.0016), but not in the QD group compared with placebo (odds ratio 1.17 [95% CI: 0.80, 1.71], p=0.4287). There was also a statistically significant reduction in FDG uptake in active segments of the qualifying artery in the BID group compared with placebo (difference -0.10 [95% CI: -0.19, -0.02], p=0.0125) and QD group compared with placebo (difference -0.10 [95% CI: -0.18, -0.02], p=0.0194) and a statistically significant reduction in the length of active segments in the BID group compared with placebo (ratio 0.56 [95% CI: 0.33, 0.95], p=0.030), but not in the QD group compared with placebo (ratio 0.59 [95% CI: 0.35, 1.00], p=0.0507).
- There was a statistically significant difference in change from baseline to Day 84 in maximum standard uptake value for visceral fat in the BID group compared with placebo (difference -0.05 [95% CI: -0.09, -0.01], p=0.0177), but not in the QD group compared with placebo (difference -0.02 [95% CI: -0.06, 0.03], p=0.5022). No changes were observed between groups in subcutaneous fat.
- There was a statistically significant decrease in average hsCRP over the 84-day treatment period in the BID group compared with placebo (ratio 0.72 [95% CI: 0.54, 0.95], p=0.0230), but not in the QD group compared with placebo (ratio 0.80 [95% CI: 0.60, 1.06], p=0.1202).
- There was a statistically significant decrease for the following plasma biomarkers in the BID group compared with placebo: MMP9, MMP9 NGAL, homocysteine, IL 8 and MCP1. None of the comparisons for the QD group versus placebo were statistically significant.
- Adverse events were reported for 29 (85%), 28 (85%) and 31 (97%) subjects in the losmapimod 7.5 mg BID, losmapimod 7.5 mg QD and placebo groups, respectively. The most commonly reported AEs were headache and diarrhea: headache was reported by 7 (21%), 10 (30%) and 10 (31%) subjects and diarrhea was reported by 8 (24%), 3 (9%) and 3 (9%) subjects in the losmapimod 7.5 mg BID, losmapimod 7.5 mg QD and placebo groups, respectively. One fatal SAE, road traffic accident (considered by the investigator to be unrelated to investigational product) was reported in the placebo group. Non-fatal SAEs were reported for 4 (12%), 1 (3%) and 2 (6%) subjects in the losmapimod 7.5 mg BID, losmapimod 7.5 mg QD and placebo groups, respectively.
- Mean trough plasma concentrations of losmapimod were approximately 3 to 4 fold higher in the losmapimod 7.5 mg BID group than in the losmapimod 7.5 mg QD group on Days 28, 42 and 84.