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Title: The p38 MAP kinase inhibitor dilmapimod ameliorates airway inflammation induced by ozone challenge in healthy volunteers

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Body: Background: p38 mitogen-activated (MAP) kinase may be involved in inflammatory airway diseases. We studied the effects of the selective oral p38 MAP kinase inhibitor SB-681323 (Dilmapimod) on airway inflammation induced by ozone challenge. Methods: This was a double-blind, randomized, four-period, cross-over study with two doses of Dilmapimod (5 mg, 25 mg), Prednisolone (50 mg), and Placebo in healthy ozone responders (increase of neutrophils by >10% in sputum after inhalation of 250 ppb ozone for 3 hours with intermittent exercise). Study drug was administered 30 minutes prior to each ozone challenge. Induced sputum was collected 3 hours after the ozone challenge for measurement of neutrophils, interleukin-8 (IL-8), and myeloperoxidase (MPO). Treatment periods were separated by a 14 days wash-out. Results: 16 subjects were randomized and 11 subjects completed all treatment periods. There was no evidence of a statistically significant difference for the number of neutrophils in sputum between Placebo and any active treatment. Relative to Placebo, statistically significant reductions of MPO and IL-8 levels in sputum supernatant were observed after treatment with Dilmapimod 25 mg and Prednisolone. Inferences based on an exploratory population of 14 subjects with sufficient sputum quality indicated a statistically non-significant reduction of neutrophils by 38%, 31% and 26% in subjects treated with Prednisolone, Dilmapimod 25 mg and Dilmapimod 5 mg, respectively. Conclusion: Dilmapimod ameliorates ozone-induced airway inflammation. Further studies in appropriate patient populations are needed. The Study was funded by GSK (GSK number SB-681323/10).