Reviewer's report

Title: Safety and efficacy of inhaled calcium lactate PUR118 in the ozone challenge model - a clinical trial

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Reviewer: Pierluigi Paggiaro

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Major points

The only point that the author should mention in the discussion is the real possibility to modulate with some pharmacologic intervention the acute response to ozone. This stimulus is quite strong, and the potential inhibitory effect of other drugs should be mentioned. Considering the controversial effect of corticosteroids and other drugs on this acute inflammatory response, the probability to significantly prevent acute neutrophilic recruitment in the airways is not particularly high. Previous experience with other drugs should be reported.

Minor points

Introduction. The potential usefulness of PUR118 in the management of airway diseases is not very clear: if the compound may protect from epithelium damage induced by oxidant or other pollutants, the possibility of modifying airway inflammation when already present is less evident. Therefore, the translation from a positive effect on the ozone-induced acute inflammation in healthy subjects to the potential usefulness in stable COPD is not correct. This should be mentioned in the introduction and probably better expanded in the discussion.

Methods. Some details in the study design are not clear: a) salbutamol was always administered before ozone exposure? why (considering the functional airway response to ozone in normals is not particularly relevant, and that salbutamol may modify the acute response to ozone)? the explanation for that has been done in the discussion, but it should mentioned also here; b) in the three treatment periods, two visits are reported while the days seem to be 3: this is not clear.

Results. In my opinion, it is not correct to put the safety data before the efficacy data, this seems to stress that the main outcome of the study was safety, but this can not be obtained with a small number of subjects. For the efficacy data, these are reported in a fairly long details, considering that a clear difference in sputum cell counts and other soluble mediators seems very small, in general not significant, and without any consistency. They might be better summarized.

Discussion. All the data reported on the effect of PUR118 seem to be obtained in experimental models or in normal subjects, these effects might be different in COPD patients with alterations in the epithelial barrier and lining fluid. The repeatability of ozone challenge should not be derived from the comparison between baseline and low dose PUR118, but from previous studies showing that
the test is reproducible in terms of respiratory function and sputum neutrophil changes.