Reviewer's report

Title: Physiological Effects of Ghrelin in Cachectic COPD: substudy of a multicenter, randomized, double-blind, placebo-controlled trial of ghrelin treatment

Version: 2 Date: 16 February 2013

Reviewer: Joseph Gertner

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Miki et al BMC Pulmonary Medicine

1. The authors describe a substudy of a larger trial of the effect of combining intravenous ghrelin injections with pulmonary rehabilitation (PR) in COPD patients defined as cachectic.

2. The double blind, placebo controlled study was conducted in over half the subjects participating in the main study, data from which are already published.

3. Objectives were to determine whether exercise capacity, defined as VO2, would be influenced by ghrelin and whether the perception of dyspnea, catecholamine levels, and various cardio-respiratory parameters would show a response.

4. The study was relatively small (n = 20 for the combined treatment groups) and the time allotted for treatment was brief, 3 weeks, which is shorter than that recommended for PR. The categorization of Japanese subjects with BMI ≤21 as "cachectic" is also questionable (see).

5. Cardiopulmonary testing showed the addition of ghrelin to significantly increase peak VO2. However, reduction in dyspnea intensity was not significantly different between treatment groups.

6. Cardiorespiratory data for "iso-time" and "iso-oxygen" are also presented but these sampling techniques are not described in the protocol. This should be explained in the text. The authors should also define what is meant by "endogenous ghrelin" in plasma measurements and how this was distinguished from circulating exogenously administered ghrelin.

7. The discussion recognizes the limitations of the study. However the conclusion should be modified to take account of the short-term nature of the study and the gap between the physiological findings and measures of direct patient benefit. The recent publication of a longer and larger trial of ghrelin in COPD-associated cachexia should also be referenced.

Items 1-5 do not require changes or could be the subject of Discretionary Revisions. Items 6-7 are categorized as "Minor Essential Revisions".
**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.

**Declaration of competing interests:**

Until January, 2013 I was an employee of Asubio Pharmaceuticals Inc, a subsidiary of Asubio Pharma Ltd of Kobe Japan. Prof. K Kangawa, senior author of the paper under review, had a scientific and commercial interest in the development of ghrelin as a treatment for various indications including COPD-associated cachexia. I am now retired and have no connection with Asubio and do not feel that my former relationship constitutes a conflict of interest for the purposes of this review.

I am co-author of a recently published paper describing a clinical trial, performed while I was at Asubio, of ghrelin in COPD-associated cachexia.