Reviewer's report

Title: A Forced Titration Study of the Antioxidant and Immunomodulatory Effects of Ambrotose AO Supplement

Version: 1 Date: 20 April 2009

Reviewer: Mohammad Abdollahi

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Abstract:
The main objective is claimed to determine the optimal dose for phase 3 clinical trial so this means that the study is a phase 2 study that should be tested in patients not healthy volunteers. According to rules of drug approval every 4-phases of clinical trial of a drug has specific definition and criteria. This study cannot be categorized as phase 2 unless described and matched with rules.

The same problem exists for the statement open label phase 1 and 2 study as mentioned in methods. Number of participants does not match with the rules if it is a phase 2 study.

Background:
Refs 1-3 are old and regarding the growth of the science in this filed, they need updating. Authors are recommended to prove the importance of antioxidants in some chronic diseases like IBD, diabetes, osteoporosis; and etc. The following new papers might be useful:


Abdollahi et al. Role of oxidative stress in osteoporosis. Therapy 2005, 2(5): 787-796. DOI: 10.1586/14750708.2.5.787


Authors are recommended to give information of the tested mixture and its
approval profile; for example its toxicity or animal study data; since authors state that it has been in use in USA; so what was the approval data from FDA; No previous report about the test compound has been addressed; this means that the present article is the first report on this drug; why? Has this drug been applied for IND? Is it a patent or licensed compound?

The open label forced titration design needs description and clarification in page 5.

What is the background to test this compound in smokers?

What is the current knowledge about dosage and administration of this drug since it is used currently; what was the previous knowledge?

Methods:

As I read I didn’t understand how have the participant be examined by a physician for their healthy parameters?

Again, it needs clarification why healthy smoker and non-smokers have been selected? What was the criteria in selecting only 20 persons?

Some immunologic parameters have been tested as secondary outcomes; readers need to understand what was the criteria for selecting them? for example what is their relation with health or oxidative stress or aging or smoking or antioxidants? for example why TNF or ILs have not been selected?

The selection criteria needs clarification about number of male or female or their age.

Results and Discussion:

Since the main aim of this study was to determine the optimum dose of the test compound, thus needs more explanation and better conclusion to convince readers what is now the best dose?

Also, authors should state the protocols for the next work that they claim it is phase 3;

Also regarding no previous report about this compound and no preclinical data or even phase 1 study, authors should clarify the status of the present work and its place in drug approval rules by considering for example FDA approval protocols.

In legends of figures and tables, the baseline 1 and 2 should be defined.

Table 2-5 can be merged.

Figure 1 and 2 show that SEs are too much; first question is why? and then how affects statistical comparisons: third question is why statistical symbols do not exist in figures