Author’s response to reviews

Title: Clinical and Genomic Safety of Treatment with Ginkgo biloba L. leaf extract (IDN 5933, Ginkgoselect®Plus) in Elderly: A Randomised placebo-controlled clinical trial [GiBiEx].

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BCAM-D-17-00213: ‘Clinical and Genomic Safety of Treatment with Ginkgo biloba L. leaf extract (IDN 5933, Ginkgoselect®Plus) in Elderly: A Randomised placebo-controlled clinical trial [GiBiEx]’ by Stefano BONASSI et al.

Dear Dr. Liu,

Thank you for these additional remarks. Our response to reviewers’ comments is attached.

Yours sincerely,
On the behalf of all authors

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Reviewer #1 (Shungte Kao):  

1. The most commonly used in evaluating hepatotoxicity are AST, ALT, bilirubin, ALKP, GGT, albumin/globulin, and prothrombin time. AFP is generally used for detection of hepatocellular carcinoma.

We selected those markers of hepatotoxicity which in the scientific literature have been consistently associated to the risk of hepatocellular carcinoma (HCC) and that were more suitable in the context of our study. As regards AFP the choice was a little more complex.

Surely AFP has been considered the main serological marker used in the diagnosis of HCC, since it is secreted by about half of HCC tumours [Lancet 379 (2012) 1245–1255; World J. Gastroenterol. 22 (2016) 262–274]. However, apart from HCC, increased plasma concentrations of AFP are reported in non-seminomatous testicular cancer. AFP concentrations are also increased in the non-tumour context, and have been described in patient with viral hepatitis or liver fibrosis. Increased AFP levels have also been described in some neurodegenerative diseases [reviewed in Clinica Chimica Acta 463 (2016) 39–44]. Like for most circulating tumour markers, this raises a dual problem of sensitivity and specificity for the diagnosis of HCC. Given these limitations, the AFP assay was withdrawn from the diagnostic criteria recommended by the “American Association for the Study of Liver Disease” (AASLD) and the “European Association for Study of the Liver” (EASL) [Hepatology 53 (2011) 1020–1022; J. Hepatol. 56 (2012) 908–943].

Therefore, given the nature of the patients in the study, to avoid the risk of false positive reports we decided to not include AFP in the list of biomarkers examined in our trial.

2. As the author presented the literature, showing that Ginkgo biloba extract caused cancers of the liver in male and female mice. So early indication of an increased risk of liver cancer
was their first safety concern; therefore, this clinical trial design was a rather controversial design. We believe that clinical trials should not be the primary consideration for liver cancer for hepatotoxicity.

Actually, pre-clinical studies are the most indicated approach to start investigating the risk of disease associated to a medical treatment. However, in this case several experimental studies have been carried out on the possible role of GBE in liver carcinogenesis. These studies were generally negative, but we believed that – given the practical impossibility of performing a clinical study on HCC - a RCT, using validated markers of liver cancer, was the most suitable study design to provide the missing piece of information on the effect of GBE in humans.

JOHNSON STANSLAS (Reviewer 2): General comments

To my question "'Is 6 months trial sufficient to provide the safety profile of this product when in reality it is consumed for a longer time? Do note that the toxicological study by US National Toxicology Program was done for 2 years!'", the author responded with the following: "This one is not a study on the possible carcinogenicity of GBE, but a safety study in which early events of genomics risks are evaluated. As regards the micronucleus and the comet assays, there is extensive literature that even an exposure of few days may alter the background frequency of DNA damage". In view of this, I would like the author to clearly incorporate this response in the revised manuscript.

In the revised Manuscript (Section: Discussion) at page 13, lines 17-21, we reported the above phrase.

As regards the possible criticism that the duration of the trial should have been longer, we have consider that the outcome of this safety study was not the possible carcinogenicity of GBE, but the early events of genomics risks. As regards the micronucleus and the comet assays, there is extensive literature that even an exposure of few days may alter the background frequency of DNA damage.