PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (see an example) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below. Some articles will have been accepted based in part or entirely on reviews undertaken for other BMJ Group journals. These will be reproduced where possible.

ARTICLE DETAILS

TITLE (PROVISIONAL)	**Viusid, a Nutritional Supplement, Increases Survival and Reduces Disease Progression in HCV-Related Decompensated Cirrhosis. A Randomized and Controlled Trial.**
AUTHORS	Vilar Gomez, Eduardo; Sanchez Rodriguez, Yoan; Torres Gonzalez, Ana; Calzadilla Bertot, Luis; Arus Soler, Enrique; Martinez Perez, Yadina; Yasells Garcia, Ali; Abreu Vazquez, Maria

VERSION 1 – REVIEW

REVIEWER	***Angelo Iacobellis, MD*** Division of Gastroenterology and Digestive Endoscopy "Casa Sollievo della Sofferenza" Hospital, IRCCS, San Giovanni rotondo, Italy No competing interest.
REVIEW RETURNED	20-Apr-2011

GENERAL COMMENTS	The topic of this work is of relevant clinical interest both, for HCV cirrhotics who failed to achieve SVR, and for decompensated cirrhotics with genotype 1 and 4 in which antiviral therapy is not recommended with the consequence of no effective therapeutical chance, except the supportive therapy. The authors showed that the Viusid therapy is able to improve survival, risk of HCC, and disease progression after a 2 year of drug consumption. Moreover, the suggested role of Viusid to improve the qualitative neutrophil function in cirrhotics notoriously characterized by an acquired immunodeficiency deserve future considerations. Recent report has shown that in decompensated cirrhosis, to achieve SVR does not signiìficantly modifiy the rate of HCC development compared to control group (not SVR group) after a long term follow up (Iacobellis 2011). Thereby, even considering the relative low number of patients enrolled in the study, it would be of interest to evaluate the cumulative risk of disease progression and HCC development splitting the patients in their different pre-treatment Child score. By this way, It might be seen that those patients with advanced Child would benefit less than those in the early stage of the cirrhosis, reconsidering the therapeutical power of Viusid after a particular histo-clinical step of the disease. If the suggested analysis would show a benefit even in the advanced Child score of functional activity and decompensation, it would become inalienable to effort future studies with a larger cohort of patients.

REVIEWER	***MOISES DIAGO***

	HEAD OF LIVER DISEASES SECTION HOSPITAL GENERAL UNIVERSITARIO VALENCIA SPAIN
REVIEW RETURNED	24-Apr-2011

RESULTS & CONCLUSIONS	-The results with Viusid (a mix of antioxidant susbstances) are excellents in order to avoid diseases progression and HCC and improving survival. This challenge has not been achieve by other drugs (inclusively antivirals) and it is difficult to understand.However the study is well designed and all the parts are well developped and presented.It mut be published.
GENERAL COMMENTS	This is an excellent research in a difficult group of patients .The results of Viusid are extremely goods and we do not know the exact mechanism of action. The small number of the sample is a limitation for the studyl considerer the resuls must be validated in a higher number of patients and by other authors.

REVIEWER	***Tahany Awad, MD*** Cochrane Hepato-Biliary Group, Denmark
REVIEW RETURNED	02-May-2011

THE STUDY	I would like to than the authors for thier hard work. This a an important study for chronic HCV patients. Current standard of treatment by peginterferon plus ribavrin has less than 50% success rate. The rate of viral clearance is much lower for patients with decompensated cirrhosis. However, by go back to clinicaltrial.gov I can't help to wonder why were the outcome changed in wording and priority "Primary Outcome Measures: The mortality secondary to liver failure at 96 weeks. Secondary Outcome Measures: The complication rates during the treatment. The hepatitis-related quality of live during the treatment. Clinical Activity Index during the treatment. The hepatocellular carcinoma incidence during the treatment. " into "Primary and secondary end points were comparisons of overall survival (OS), time to disease progression and time to hepatocellular carcinoma (HCC) diagnosis between groups in the intention-to-treat population." Further, the manuscript need revision. The introduction is rather long and redundant with an overall poor language in the whole manuscript.
RESULTS & CONCLUSIONS	This trial has a small sample size (100 patient) and with a discontinuation rate of 33%, ome must be suspecting and careful when drawing conclusion from this trail. The results and the discussion need to be more clear and precise.

VERSION 1 – AUTHOR RESPONSE

Thanks once again to reviewers for their excellent considerations and analyses in relation to different topics into the paper.

In response to reviewer comment 1: Angelo Iacobellis, MD

1. Thereby, even considering the relative low number of patients enrolled in the study, it would be of interest to evaluate the cumulative risk of disease progression and HCC development splitting the patients in their different pre-treatment Child score. …….

We have computed these analyses according to the excellent suggestions of the reviewer Dr. Iacobellis. These subgroup analyses have been performed using the Child-Pugh classification in two groups (Child-Pugh class A versus B plus C), attributable to presence of a small number of patients and events in the group of Child-Pugh C. However, the results should be considered with caution because of small sample size of the trial.

Figures 2A, 2B, 2C of the originally submitted paper have been deleted and substituted by the Figure 2A (Survival according to Child-Pugh classes) and Figure 2B (Disease progression according to Child-Pugh classes).

A stratified analysis for the cumulative incidence of HCC according to Child-Pugh classes was not performed, due to a small proportion of patients with presence of HCC which could generate a bias in the interpretation of the results.

The information of the previous figure 2A, 2B and 2C is provided in the Table 3.

In response to reviewer comments 3: Tahany Awad, MD

1. However, by go back to clinicaltrial.gov I can't help to wonder why were the outcome changed in wording and priority……

The primary outcome of the study was survival or mortality. Survival is a more precise and reasonable aim and it can be comparable in percentage with the rest of the studies evaluating the natural history or the impact of treatment strategies on survival of patients with cirrhosis.

The current secondary outcomes included the time to disease progression, time to diagnosis of HCC, time to worsening of the prognostic scoring systems Child-Pugh and MELD, time to a new occurrence or relapse for each one of the main clinical complications secondary to portal hypertension, and safety.

The complication rates during the treatment were redefined and evaluated for the analysis as a new occurrence or relapse for each one of the main clinical complications secondary to portal hypertension because it is a more precise and less subjective terminology to assess time dependent clinical complications in cirrhotic patients.

The hepatocellular carcinoma incidence during the treatment was redefined for the analysis as time to diagnosis of HCC, because it is a more accepted terminology in the current studies.

The time to disease progression is a mixture of clinical complications or complication rates with diagnosis of HCC and it were defined in the study protocol.

The hepatitis-related quality of live during the treatment was assessed using The Hepatitis Quality of Life Questionnaire (HQLQ) – SF 36 v2 (Standard form), but the results will be submitted as another paper together the impact of viusid on the clinical activity index of HCV-related cirrhotic patients.

2. Introduction was shortened and reviewed.

VERSION 2 - REVIEW

REVIEWER	***Angelo Iacobellis***
REVIEW RETURNED	18-May-2011

THE STUDY	The number of patients should be higher to better define the efficacy of the drug in this subset of cirrhotic patients. Indeed, these patients at late stage of disease usually receive different supportive treatment that should be considered in a larger trial.

RESULTS & CONCLUSIONS	Even I have doubts that Viusid could significantly modified the natural history of a decompensated cirrhotic if better stritified I can only accept this data waiting for further studies.
GENERAL COMMENTS	This pilot study on Viusid administration in cirrhotic patients appears to show an improvement in both cumulative risk of disease progression and survival probability in those patients with Child B and C of decompensated disease. No benefits of Viusid have been shown in those patients with lower advanced disease giving the idea that the efficacy of this drug is inversely correlated to the stage of disease acting much more on the complications correlated to the decompensated stage. If this concept would be further demonstrated by a large cohort patient trial, Viusid could be considered a useful drug in preventing worsening of liver function activity in a subset of patients with no alternative treatment but symptomatic.

VERSION 2 – AUTHOR RESPONSE

Thanks for give us once again the opportunity to resubmit the revised manuscript.
Thanks once again to reviewers for their excellent considerations and analyses in relation to different topics into the paper.
In response to editor-in-chief comments:
1. All cited studies regarding Viusid are linked to your research centre. Please confirm that your institution has no financial interest in Viusid.
All studies related to viusid have been investigator-initiated researches, and Catalysis had no direct involvement in the design of the study, data collection, or preparation of the manuscript. The National Institute of Gastroenterology had no financial interest with the nutritional supplement viusid.
The last statement was inserted on the manuscript in the funding statement.

2. Please include in the Methods section information regarding why the primary outcomes for the study were changed, compared with the registered protocol.
This statement was inserted and highlighted in the Methods section (Definition of outcomes).
3. Please briefly review, in a paragraph, what previous studies have shown about this supplement's formulation, effectiveness, and safety (including any harms).
The information of effectiveness and safety of viusid, reported by previous studies, was inserted in a paragraph in the introduction section. Only three RCT have evaluated the efficacy and safety of viusid in patients with chronic liver disease and it are referenced in the submitted paper.
4. The name 'Viusid' is repeated extensively throughout the manuscript. If no generic name exists, please edit to reduce the frequency of use of the term 'Viusid'. Please state which active ingredients it contains, and in which proportions.
There is no generic name for viusid. The name of viusid was changed by experimental group, experimental intervention, nutritional supplement or active product through the manuscript. Theses changes were highlighted. In the introduction section was mentioned that the glycyrrhizin (0.033 g) is the most important active ingredient of the supplement. It is known to have various immune-modulating, antiviral and biological response-modifier activities and these properties were briefly mentioned in a paragraph in the introduction. New references were included to support the glycyrrhizin properties.
5. The abstract should state the primary outcome very clearly. At the moment it combines primary and secondary outcomes.
The primary and secondary outcomes were clearly stated in the abstract.
6. We agree with the comments of the professor Angelo Iacobellis in relation to design a multicenter and multinational study with a large proportion of patients with HCV-related decompensated cirrhosis in particular those with CP classes B or C to support the preliminary results obtained in this pilot study.
Thanks once again for their interesting and helpful comments.