Reviewer's report

Title: Hepatic profile analyses of tipranavir in Phase II and III clinical trials

Date: 26 May 2009

Reviewer: Marina Nunez

Reviewer's report:

A) Major compulsory reviews:

1. In my view, hepatic Serious Adverse Events (SAE), and more specifically Hepatic Failure (HF) is the most important clinical aspect of the paper. Therefore, I miss a more detailed information on those cases. I suggest to add a table with the information (as complete as possible), which should include:
   - time of onset,
   - baseline CD4 counts,
   - CD4 increase while on TPV,
   - for the cases labeled as -LD additional information on liver status (such as alcohol related or non-alcoholic steatohepatitis-cirrhosis) which seem to have been present in some -LD cases (and also, reconsider the definition of -LD and +LD),
   - for the cases labeled as +LD, presence or absence of cirrhosis, HBV and or HCV replication status
   - HF attributable to TPV-based HAART or not (since it is stated that HF patients had dMAC, visceral leishmaniasis, sepsis, etc….) It needs to be made very clear if the TPV could have had anything to do with the HF or not.

   In addition to the table it is very important that the authors address the risk factors for it (viral hepatitis seems to be one) and make an statement to that respect with the corresponding level of certainty and on the relationship of TPV with HF (unlikely, possible, likely, etc…) 

2. Comments to the abstract:
   - The presentation of the results is confusing. Please present the figures on asymptomatic events including associated risk factors, and thereafter SAE-HF, instead of talking about DAIDS, then SAE and then again TE. The abstract includes lots of data, some of them unnecessary, and omits some aspects that are more relevant to the reader. The incidence of grade 3-4 TE in +LD should be included. Also, the incidence of HF is important in the abstract.

   - Under results, please avoid to “commenting” the data presented. Words such as “low”, “just”, “most” and “only” should be removed. Instead, limit yourselves to convey the data.

   - The conclusion does not convey the “core” of the data reported in the article,
which in my view are the cumulative incidence of grade 3-4 TE according to +LD / –LD and of HF and risk factors.

3. In the introduction, first sentence of 2nd paragraph: 30% incidence of TE in previous reports seems a little to high unless the authors are talking about incidence in a cohort of co-infected patients. Please, provide a range of HAART-related transaminase elevation, including more recent references (one of the 2 provided is from 1998). It has been highlighted in a review that the reported incidences range from as low as 2% (Nunez, J Hepatology 2006).

4. Under methods, last paragraph. Please provide the definition of normal transaminases, i.e., AASLD definition versus other.

5. Results. Risk factors for grade 3-4 TE. It is stated that “significant factors….. were coinfection, baseline transaminases and baseline CD4 (table 3). However, based on table 3 data only TPV and coinfection are statistically significant (“1” is included in the interval of 95% CI for baseline transaminases and CD4>200).

6. Results. Clinical hepatic SAE, 2nd paragraph. The description of +LD SAE is confusing: what do the patients mean by “hepatocellular damage”? And by “hepatotoxicity or toxic hepatitis”? And by two patients had steatosis or cirrhosis: how many had steatosis and how many cirrhosis? Is the presence of steatosis enough reason to classify the elevated TE as SAE given the relatively high prevalence of staetosis among HIV+ pts? In like manner, isolated hyperbilirubinemia migh be a non-hepatic event. How a –LD pt is then found to have cirrhosis?: please revise classification of –LD and +LD.

B) Minor compulsory reviews:

- In the abstract, please define DAIDS.

- It is confusing to use two terms which appear to represent the same thing: DAIDS and TE.

- In the introduction, last sentence of 2nd paragraph: immune reconstitution, one of the mechanisms of ALT elevation on HAART, is mentioned. It is unclear the purpose of mentioning this particular aspect of HAART ALT elevation and no other mechanisms.

- Methods, 1st paragraph pg 9: please provide the complete word for K-M: Kaplan-Mayer. Please, provide the statistical package used for the analyses as well as the definition of statistically significant p values.

- Results, 1st sentence. Since the paper focuses on hepatic events, it makes more sense to provide the figure of 11.1% pts who developed grade 3-4 transaminase elevation, instead of 88.9% who did not. The same applies to the 1st sentence under “clinical outcomes following grade 3-4…..”

- Results: please refrain from commenting on the results, e.g., “the majority (84%)…..” “only four developed…”. It seems more appropriate for this section to just presenting the numbers without adding if they are high, low, or etc.…

- Table 3: please, provide exact “p values”. It is very unusual to report as <= 0.07.

- Table 4 does not provide additional information over the test. I suggest to delete
-Figure 1. Please provide “p values”

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

No