Author's response to reviews

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

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Author's response to reviews: see over
Dear BioMed Central Editorial Team:

Thank you for the favorable response to our paper. The manuscript was changed according to the comments and suggestions received. We are enclosing our responses to each of the comments by the reviewers. The responses are numbered according to the originally numbered comments by each of the reviewers.

We are looking forward to hearing from you soon.

Thank you

Kind Regards

Jaromir Mikl
Response to reviewers' comments:

- **Dr. Nicola Abrescia:**

  1. A paragraph in the limitations within the discussion section with additional references was added to address the issue of low number of female patients included in these clinical trials.

  2. Although the safety of patients was of paramount importance, the main focus of these trials was efficacy in HIV patients with highly advanced disease and no treatment options other than tipranavir. As such, the collection of all predisposing risk factors for hepatotoxicity was not systematically ascertained as it was patient or investigator reported. Consequently, we feel that hypersensitivity or allergic predisposition was underreported. In these trials only 25 (1.9%) of the 1299 patients self-reported Drug Hypersensitivity. We agree with Dr. Abrescia that allergic predisposition is a potential risk factor for hepatotoxicity, however, in our patient cohort too few patients reported this risk factor in order to include it in our analysis. This was added to the discussion section of the article.

  3. As stated in answering comment 2, above, the ascertainment for hepatic steatosis at entry into these trials is also incomplete. In addition, one of the inclusion/exclusion criteria for these trials was to exclude patients who abused alcohol and further information on alcohol use was not collected. Thus we would expect a low prevalence of alcohol related hepatic steatosis. Together with the low prevalence of HCV coinfection, the number of patients presenting with any hepatic steatosis at study entry was too small to warrant evaluation of this important risk factor. Only 6 (0.5%) of the 1299 patients self-reported hepatic steatosis. This statement was added to the discussion section.

  4. Per protocol, any patient experiencing DAIDS 4 toxicity was to be discontinued from treatment. However, the patient population consisted of patients with advanced stage of HIV disease, presenting with opportunistic infections and the TPV/r was their last option for treatment. These compassionate trial designs were developed and approved by the regulatory authorities and key opinion leaders and continued treatment despite toxicity was a decision between the principal investigator and the patient on a case by case basis with very close patient monitoring.

  5. The references were corrected to indicate the specific conferences at which the referenced abstract were presented.
Dr. Marina Nunez:

A. Major compulsory comments:

1. Baseline information on hepatic SAE cases was added to Table 1 and additional text was added to the 'Baseline characteristics' section of this article.

   Although the safety of patients was of paramount importance, the main focus of these trials was efficacy in HIV patients with highly advanced disease and no treatment options other than tipranavir. As such, the collection of all predisposing risk factors for hepatotoxicity was not systematically ascertained as it was patient or investigator reported. The inclusion/exclusion criteria were designed to exclude any patients who abused alcohol from enrollment and no further information on alcohol use was collected in these trials. In addition, these trials were not originally designed to capture information on hepatic steatosis as a predisposing risk factor for hepatotoxicity. As a result, the prevalence of hepatic steatosis at baseline is expected to be low and the distinction between alcohol or non-alcohol steatosis classification is not possible. At baseline, only 6 (0.5%) of the 1299 patients self-reported hepatic steatosis; 5 among the -LD patients (5/1088, 0.5%) and 1 among the +LD patients (1/179, 0.6%). The very low number of patients reporting hepatic steatosis precludes any meaningful analysis and interpretation. These limitations are now discussed in the ‘Conclusion’ section.

   +LD patients: The HBV and/or HCV co-infection status by patient risk group is displayed in Table 1 of the document. One patient (1/179; 0.56%) was reported with hepatic cirrhosis (MedDRA Preferred Term).

   Six patients had the preferred term hepatic failure, for an overall exposure adjusted incidence of 0.3/100 Person Years of Exposure (PEY) and unadjusted incidence of 0.5%. Two of these cases occurred among hepatitis co-infected patients (1.0/100 PEY or unadjusted 1.4%) while four occurred among non-hepatitis co-infected patients (0.2/100 PEY or unadjusted 0.4%). These patients had profound immunosuppression and the rate appears higher among hepatitis co-infected patients. In all but one case, the extent of the role of TPV in the development of liver failure is uncertain. Similar text was added to the results section of the publication.

2. The results section in the abstract was re-written according to the suggestion by Dr. Nunez.

   Words such as 'low', 'just', 'most' were removed from the abstract.

   The conclusion section of the abstract was re-written to reflect the 'core' results as suggested by Dr. Nunez.

3. The first sentence of the 2nd paragraph of Introduction section was changed as suggested by Dr. Nunez and an additional reference was included.
4. The definition of all 4 categories of the DAIDS toxicity grades was included in the text.

5. The text was changed to reflect the significance of risk factors for TEs, per Dr. Nunez.

6. In describing the co-morbidity reported among patients with SAEs, the authors used the MedDRA Preferred Terms version 8.1, as provided by the principal investigators. Furthermore, the ICH definition of an SAE: "Any untoward medical occurrence that at any dose: results in death, is life-threatening, requires inpatient hospitalization, or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect", as determined by the investigators for each case, was used in the conduct of these trials.

The sentence of how many patient had steatosis and how many cirrhosis was rewritten for clarification.

The authors would like re-iterate that the classification of patients into either low risk (-LD) or high risk (+LD) groups was accomplished by risk factors identified retrospectively based on hepatitis co-infection and/or elevated transaminases at baseline. In the text, the cases and their co-morbidities being described are treatment emergent and were diagnosed during the course of the study.

B. Minor compulsory reviews:

- DAIDS was defined in the abstract
- Consistency of terminology used was applied (DAIDS and TE)
- The reference to Immune reconstitution was removed from the Introduction section of the paper.
- The K-M was written in full as Kaplan-Meier.
- Results were changed to indicate 11.1%...
- The text in the results section was adjusted not to be evaluative but simply reporting the numbers as results.
- Table 3 was changed to include the exact p-values.
- Table 4 is instrumental for readers to be able to calculate the PPV and thus the authors feel it should remain.
- p-values were added to the footnotes for Figure 1.