Author's response to reviews

Title: Effectiveness and Safety of generic version of abacavir/lamivudine and efavirenz in treatment naïve HIV-infected patients: a nonrandomized, open-label, phase IV study in Cali-Colombia, 2011-2012

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Author's response to reviews:

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Dr. Nicola Gianotti

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Subject: Response to point that must be addressed in the revised manuscript "Safety and effectiveness of generic version of abacavir/lamivudine and efavirenz in HIV/AIDS treatment naïve patients: a nonrandomized, open-label, phase IV study in Cali-Colombia, 2011-2012" (INFD-D-16-00081)

Dear editor.

By logging on to the system, we have resubmitted the reviewed article “Safety and effectiveness of generic version of abacavir/lamivudine and efavirenz in HIV/AIDS treatment naïve patients: a nonrandomized, open-label, phase IV study in Cali-Colombia, 2011-2012" (INFD-D-16-00081)”. We had trilled to address the requests and comments. All changes (including deletions) to the text had been underlined or highlighted, and a addressing each numbered comment (with page numbers indicating the location of change).

Point to address:

1. Comment #8 has not been fully addressed: given the very small sample size it seems not reasonable to present data as means/SD; authors do not clearly explain why they still would prefer to use this modality of presentation of data for some variables.

Median (Q1-Q3) has been used to present the main results. In some cases, due to data were used to compare some safety variables, mean/SD were used. Thus, only in table 3, mean/SD were presented for lipid profile (total cholesterol, LDL-C, HDL-C, and triglycerides) and for cardiovascular risk according to Framingham score. It is denoted on tables 2 and 3.

2. Comment #17 has not been fully addressed: at least the primary end-point of the study must be specified (as well as the primary analysis). Please use the verb “to withdraw” (from the study) in place of “to remove” (from the study).

According to suggestion, the objective was adjusted both in abstract and main text. In addition, both the primary end-point and secondary end-point of the study were specified (as well as the primary analysis). In the reviewed article, it is denoted in both the abstract and the text (on page 6, first paragraph).

Abstract. The objective of this study was to describe the effectiveness and the safety of the generic abacavir/lamivudine and efavirenz in treatment-naïve HIV-infected patients.

… The primary end-point was to achieve viral load <40 copies/mL at 12 months after baseline to assess effectiveness. Secondary end-point of the study were 1) to asses increasing in T-CD4 lymphocytes levels as accompaniment to asses effectiveness, and 2) to assess both gastrointestinal, skin, and central nervous system symptoms, and lipid profile, cardiovascular risk, renal, and hepatic function as safety profile.

The verb “to withdraw” or to exclude (from the study) in place of “to remove” (from the study) was used.

3. Abstract: the primary end-point of the study is not clearly stated.

In the abstract, the primary end-point of the study was clearly stated.

4. Lines 27-32: it must be mentioned that also in Columbia Guideline ABC/3TC is recommended only if baseline viral load is <100000 copies/mL.

On page 4, in lines 27-32 it was mentioned that similar to guidelines in patients with viral load >100,000 copies/mL the use of ABC/3TC with efavirenz or atazanavir/ritonavir is not recommended, by greater likelihood of virologic failure. Thus, the following text was auditioned: “Both the Colombia [4] and WHO [5] guidelines stated that in patients with pre-treatment HIV RNA >100,000 copies/mL, the regimens ABC/3TC and EFV or ABC/3TC and atazanavir/ritonavir do not be used due to higher rates of virologic failure”

5. Lines 37-42: syntax must be reviewed.

The syntax of the following text was reviewed. “Thus, although bioequivalence of ABC/3TC and EFV generics have been determined according to Colombia regulations [13]. It is important to denote that these drugs did not have WHO prequalification which may add concerns about quality of these kind of products marketing in Colombia”

Thus, although bioequivalence of ABC/3TC and EFV generics have been determined according to Colombia regulations [13]. It is important to denote that these drugs did not have WHO prequalification medicines, which may add concerns about quality of these kind of products marketing in Colombia.

6. Lines 13-19: “Therefore, the objective was to describe the effectiveness (assessing viral load <40 copies/mL and increasing in values of T-CD4 lymphocytes) and safety (assessing gastrointestinal, skin, and central nervous system symptoms, lipid profile, cardiovascular risk, renal, and hepatic function) of the generic “…….”

On page 6, lines 13-19: Therefore, the objective was to describe the effectiveness (assessing viral load <40 copies/mL and increasing in values of T-CD4 lymphocytes) and safety (assessing gastrointestinal, skin, and central nervous system symptoms, lipid profile, cardiovascular risk, renal, and hepatic function) of the generic……." Was change to "Therefore, the objective of the present study was to describe the effectiveness and the safety of the generic of the generic version of ABC/3TC and EFV in treatment naïve HIV-infected patients attending a program that provides complete outpatient consultation and continuing care for patients with HIV/AIDS".

7. Methods: please state:

a. If the study is monocentric.

In methods (Research design), it was specified that the study was monocentric. Thus, the following text was added: "The present study was monocentric, nonrandomized, open-label, phase IV study in treatment-naïve HIV-infected patients 18 years or older with indication to receive combination antiretroviral therapy (cART) containing ABC/3TC and EFV".

b. Which RT-PCR assay has been used to assess viral load? (and specify if testing was centralized, performed on frozen samples rather than as soon as blood was drawn).

According to suggestion, the following text was added:

Viral load was quantified by real-time reverse transcriptase PCR (RT-PCR) Abbott Real Time HIV-1 m2000 assay (Abbott, Chicago, IL). Blood samples were collected by a certified technician and processed in a centralized national reference laboratory. PCR testing was performed on frozen samples rather than as soon as blood was drawn.

c. Which was the primary end-point of the study?

In methods (abstract and the text), both the primary end-point and the second end-point of the study were added: "The primary end-point was to achieve viral load <40 copies/mL at 12 months after baseline to assess effectiveness. Secondary end-point of the study were 1) to asses increasing in T-CD4 lymphocytes levels as accompaniment to asses effectiveness, and 2) to assess both gastrointestinal, skin, and central nervous system symptoms, and lipid profile, cardiovascular risk, renal, and hepatic function as safety profile"

d. Which equation was used to calculate the cardiovascular risk? (guess Framingham looking at results, but this must be specified in the methods).

It had been specified in methods: In inclusion criteria say: … iii) cardiovascular (CV) risk assessed as low (<10%), using the Framingham risk score [20]. However, according to suggestion if was again specified in methods (to assess drug safety) … and CV risk assessment, using the Framingham risk score [20]…

e. Also, in the statistical methods, it must be mentioned how ITT and OT analyses were performed and which one was the primary analysis.

According to suggestion, at the end of the statistical methods, the following text was added: "The primary analysis was the proportion of patients who viral load <40 copies/mL at 12 months after baseline to assess effectiveness. Both intention to treat (ITT) analyses (consider all the subjects included at the beginning of the study) and on treatment (OT) analyses (consider only the subjects who fulfill completed the 12 months of follow-up) were used to analyze the results".

f. Discussion: the discussion is now far too long (almost seven pages!): it must be shortened to four pages maximum; many concepts and data can be summarized. Furthermore, please avoid comparing ITT results with OT results.

According to suggestion, discussion was shortened closer to four pages.

Other changes.

1. According to integral changes, the title was adjusted to: Effectiveness and Safety of generic version of abacavir/lamivudine and efavirenz in treatment naïve HIV-infected patients: a nonrandomized, open-label, phase IV study in Cali-Colombia, 2011–2012

2. Grammar and clarity were reviewed and adjusted.

3. Coherent among abstract and text was adjusted.

Thank you for your collaboration and contribution to improve the quality of our manuscript.

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