Author's response to reviews

Title: Cost-effectiveness of posaconazole versus fluconazole or itraconazole in the prevention of invasive fungal infections among high-risk neutropenic patients in Spain

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Author's response to reviews: see over
Dear Editorial Board of *BMC Infectious Diseases*,

Please find attached the revised manuscript: “Cost-effectiveness of posaconazole versus fluconazole or itraconazole in the prevention of invasive fungal infections among high-risk neutropenic patients in Spain”, which we would like to resubmit for publication as an original article in *BMC Infectious Diseases*.

The authors would like to thank the reviewers for their time and their valuable comments. In the following pages are our point-by-point responses to each of the comments of the reviewers.

We hope that the revisions in the manuscript and our accompanying responses will be sufficient to make our manuscript suitable for publication.

We shall look forward to hearing from you at your earliest convenience.

Yours sincerely,

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Title: Cost-effectiveness of posaconazole versus fluconazole or itraconazole in the prevention of invasive fungal infections among high-risk neutropenic patients in Spain

Reviewer: Dominique Sanglard

This paper summarizes a study on the cost-effectiveness of posaconazole as compared to standards azole in the prevention of invasive fungal infection. The authors used clinical data from previous studies and implemented algorithms specific for Spanish conditions enabling cost evaluation. The authors found that posaconazole was more cost-effective than were other azoles. The data are clearly presented and well explained.

Discretionary Revisions:

1. It is not clear in the present study how costs for drugs such as fluconazole and itraconazole are split between drug costs and management costs. This is mentioned for posaconazole (p 11, bottom).

Response:

On page 11 it is specified that the total costs of treatment in the SAT group (standard azole therapy, fluconazole or itraconazole) was €7,928 per patient, €450 related to the prophylactic drug used in avoiding IFI (drug costs, administration and monitoring) and €7,478 associated with the costs of treatment of FI in the patients with neutropenia.

2. Clearly fluconazole and itraconazole are less expensive drugs than posaconazole (5-6 times), however cost effectiveness is increased for posaconazole to a lesser extent. What are the factors contributing to this difference?

Response:

The key point in the results of the model is the estimate of the costs of IFI to be compared with the extra costs of posaconazole over standard azole therapy. The average cost of prophylaxis was almost 6 times more expensive in the posaconazole group (€3,007 vs €450), but due to the fact that posaconazole prevents more IFIs than the comparator, this difference was more than offset by the decreased costs of the treatment of IFIs (€4,364 lower per patient). So, the total cost of prophylaxis is different for posaconazole and for SAT, but also is the cost of IFI. The difference between the two is what determines that the ratio of cost-effectiveness is not the same as the ratio between the drug costs. The final result was a saving of €1,807 per patient treated with posaconazole compared to the patients who received SAT prophylaxis with fluconazole or itraconazole. As posaconazole was more
effective and less costly relative to SAT, it was said to be “dominant” from a cost-effective point of view.

3. The authors used published data from clinical trials, however it would be interesting to learn about the fungal species responsible for the IFI. Clearly, in a prospective view, the choice of the antifungal would also depend on the species identified, if at all possible, causing the IFI. The cost effectiveness would also depend on the correct choice of the antifungal agent. The authors need to mention this possibility.

Response:

We have included a comment about this in page 13.

Early diagnosis of fungal infections is difficult as nonspecific symptoms (fever) are often the only sign. Furthermore, antifungal treatment of established IFI has a high failure rate (60–70%) and is very costly. As prophylaxis of IFI is now the standard practice in most hospitals for patients at high risk, a “no prophylaxis” strategy is no longer an appropriate comparison for an economic evaluation.

It is true that the ecology of the environment clearly determined the results both of prophylaxis as well as of treatment of IFI. Nevertheless, the results of RCTs are not powered to define the impact of the sensitivity of the different species on the outcome, and therefore it is not possible to ascertain what would be the impact on effectiveness, neither on cost-effectiveness, of changes in the ecology, or in the resistance pattern of the antifungal drugs assessed when it changes form the RCT sites and setting into clinical practice in a given environment.

Azoles are the most commonly used agents for antifungal prophylaxis. Fluconazole has proved to be useful to prevent and reduce the mortality due to yeast IFI in several contexts. But its major disadvantage is the lack of efficacy against *Aspergillus* species, which together with *Candida* species are the most common causes of IFI. So, in patients at high risk for IFI due to filamentous fungi, it is necessary the use of extended spectrum drugs. Itraconazole has a wider spectrum of activity than fluconazole, including activity against *Aspergillus* species, but its clinical usefulness is limited by the poor tolerability of the oral solution and the erratic bioavailability of the oral-capsule formulation. Thus, early-generation oral azole agents have limitations related to the spectrum of antifungal activity and tolerability. Posaconazole is a new-generation triazole with in vitro activity against a wide spectrum of medically important fungi, including *Candida* species, *Aspergillus* species, *Zygomycetes*, *Fusarium* species and *Cryptococcus neoformans*. Two randomized phase III trials in a total of 1,202 patients at high risk demonstrated the efficacy and safety of posaconazole compared with
standard azole therapy in the prevention of IFIs. By reducing IFIs in AML/MDS patients, the present economic analysis concluded that posaconazole is a cost-saving prophylactic strategy compared with fluconazole or itraconazole.

The deterministic sensitivity analyses answered the question of if cost-effectiveness of prophylactic posaconazole depends on the IFI risk, which can vary by hospital: for all the variations of the probability of experiencing an IFI, posaconazole is the dominant strategy over that of SAT.

**Minor revisions**

1. Please correct spelling of "fluconazol" or "itraconazol" to "fluconazole" and "itraconazole"

**Response:**

We have checked the manuscript to make sure that correct spelling is used throughout the whole manuscript
Title: Cost-effectiveness of posaconazole versus fluconazole or itraconazole in the prevention of invasive fungal infections among high-risk neutropenic patients in Spain

Reviewer: Michael Pfaller

Reviewer's report:
This paper represents the 8th such analysis of the same data the only difference being that it is from the Spanish perspective. I have serious doubts that all of this "re-analysis/re-publishing" is necessary or useful except as a marketing ploy in each country. The rationale for so many different "perspective" publications should be clearly explained by the authors. The limitations of such modeling as it pertains to the real world must also be discussed. For example is an increase in life expectancy from 2.3 yrs to 2.5 yrs really a laudable goal?

Response:

The following comment is summarized in the discussion of the manuscript.

Since controlling the healthcare budget is a major priority for Spanish national health system, decisions related to budget allocation will be based not only on efficacy and safety of the available antifungal agents but also on the associated costs. The results of the present analysis can be helpful in the decision-making process of the selection of an antifungal prophylaxis at a healthcare payer or hospital level in Spain. This impact is relevant, since it is the basis for management decision making at the regional or local level, that can greatly vary between countries, since although clinical results can be somewhat safely extrapolated from one environment or country to another, it is not the case of cost-effectiveness. For example, in this analysis the relative cost effectiveness of posaconazole is influenced by a considerable degree by the high cost of IFD treatment, so it is critical that the estimated costs of treating IFD were collected from Spanish clinical setting.

Modelled pharmacoeconomic analyses attempt to project longer-term costs and clinical outcomes by relying on a number of assumptions, using data from a variety of sources and extrapolating clinical trial results to the general population. Moreover, even if results are robust to plausible changes in key input variables, they may not be applicable to other geographical regions because of differences in healthcare systems, medical practice and unit costs. Still, these sensitivity analyses (for example, those undertaken in previous manuscripts on this same topic) do not necessarily address what the outcomes would be in Spain, and are usually not accepted locally as valid evidence in this regard.
As it was defined in the French analysis that followed this methodology, the benefit expressed in life-years gained is not as great because of the current short life expectancy of these patients and because of the scarcity of information available concerning the expected survival of patients according to the presence or absence of IFI. Still, it needs to be taken into consideration when judging these differences is that they are always average differences (actually, differences of means between groups), that are substantially higher (or lower) when applied to specific individuals, for whom can indeed be very relevant.