Author's response to reviews

Title: A Multicentre, Randomized, Double-blind Study Comparing Different FK778 Doses (Manitimus) with Tacrolimus and Steroids vs. MMF with Tacrolimus and Steroids in Renal Transplantation

Authors:

Zbigniew Wlodarczyk (kiktranspl@cm.umk.pl)
Yves Vanrenterghem (yves.vanrenterghem@uz.kuleuven.ac.be)
Bernhard K Krämer (Bernhard.Kraemer@umm.de)
Jean-Paul Squifflet (JP.Squifflet@chu.ulg.ac.be)
Marek Ostrowski (mostrowski@poczta.onet.pl)

Version: 2 Date: 12 June 2012

Author's response to reviews:

A Multicentre, Randomized, Double-blind Study Comparing Different FK778 Doses (Manitimus) with Tacrolimus and Steroids vs. MMF with Tacrolimus and Steroids in Renal Transplantation (manuscript #0314)

Reply to reviewers’ comments

Reviewer 1: Minor essential revisions

Please explain why the authors chose an MMF dose of 1g/day (i.e. rather than the standard 1g BID) for the control arm.

An earlier dose-finding study showed that 2 g MMF/day offered no benefit over 1 g MMF/day in combination with tacrolimus and steroids. Furthermore, toxicity was greater with a regimen consisting of 2 g MMF/day. Several clinical trials demonstrated a superior efficacy:toxicity ratio using 1 g MMF/day in combination with tacrolimus.

The authors state that a dose-finding study indicated that FK778 plasma concentrations >100 mcg/ml may be most efficacious yet in the present study, one of the groups had target trough levels of 50-100 mcg/ml. Please explain the choice to use this low target range when the dose-finding study suggested otherwise.

The choice for these three concentration ranges and even the lower range is based not only upon efficacy but also tolerability issues with anemia. The three drug concentrations have been selected to find optimal concentration balancing efficacy and toxicity. An explanatory sentence has now been added to the Introduction.

Please comment on the mechanism (or theoretic mechanism) behind the apparent tacrolimus:FK778 drug interaction.

The reviewer’s comment refers to a possible pharmacokinetic interaction between the drugs; i.e., high FK778 levels require increased doses of tacrolimus.
to reach and maintain comparable tacrolimus levels. Indeed, there is evidence suggesting a pharmacokinetic interaction between FK778 and tacrolimus, the exact mechanism, however, is not fully understood.

In discussing the proof of concept clinical trial (ref 7), the authors state that target plasma FK778 levels were hard to achieve in the early phase after transplantation. Please add a comment explaining why (i.e. were the levels achieved generally too high or too low?).

This point has been made clearer by adding a clause in the Introduction; the dosing schedule of the proof of concept study yielded levels <100 ng/mL in many patients.

With the inclusion/exclusion criteria, please clarify whether ECD or DCD donors were allowed and whether subjects were 1st transplant only or whether repeat renal transplant recipients were allowed. Were all pairs truly ABO identical? or were non-identical but ABO-compatible transplants allowed?

A sentence with this information has been added to the Results (please see paragraph 2, page 7).

Define HBV positive. Were these surface antigen positive?
As commonly understood, HBV positive means Hepatitis B surface antigen positive.

Reviewer 2: Major compulsory revisions

The authors should comment why 3 different groups of FK778 were chosen with overlapping target trough levels. One could have assumed that only very minor differences between groups would become apparent.

As addressed above, different target concentrations were defined in order to optimize efficacy with tolerability within a fairly narrow range. Results from the proof of concept study indicated that low FK778 levels were not effective but did not provide clear information about “optimal” FK778 levels. Overlapping target levels were chosen since it was obvious from the proof of concept study that 3 distinct level ranges were not possible.

Table 3: It is unclear how the numbers of treatment outcome (steroid resistant/steroid sensitive) are related to the BPAR at 12 months, because the numbers don’t add up.

A patient might have had more than one rejection episode (i.e., an event of steroid resistant BPAR and an event of steroid sensitive BPAR). An explanatory footnote has been added to the table.

Discussion: Although it is stated on page 10 that “The incidence of treatment failure at 12 months ... was comparable between low level [FK778] and MMF...” the authors conclude that “the incidence of treatment failure in our study was lower with MMF than with low level FK778”. That latter statement is not supported by the data.

This sentence has been revised to avoid any misrepresentation of the results. It
now reads “. . . the incidence of treatment failure was numerically lower with MMF than with low level FK778”. 