Author's response to reviews

**Title:** Study protocol of the RAND-study: a multicenter, prospective cohort study investigating response and adherence to nilotinib treatment in chronic myeloid leukemia

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**Author's response to reviews:** see over
Dear Editor,

Thank you for the peer review of our paper entitled ‘Study protocol of the RAND-study: a multicenter, prospective cohort study investigating response and adherence to nilotinib treatment in chronic myeloid leukemia’.

Below is the point-by-point response to the concerns of the reviewers.

Referee 1.
1. The primary end-point is CCyR at 12 months. Responses with Nilotinib in front line are faster and deeper, as demonstrated in ENESTnd trial (Kantarjian, 2011). In the ENEST most of patients will achieve this primary end-point at 6 months. A suggestion for this study is to consider as primary end-point the rate of MMR at 12 months.

We agree with this comment and changed the primary efficacy end-point to the rate of MMR at 12 months throughout the revised manuscript. Also, in view of the implementation of the new Dutch CML treatment guidelines, to be expected summer 2014, PCR will be used primarily to measure the response instead of cytogenetics.

2. The study will also measure Nilotinib plasma levels, but in the methods session the statistic analysis that will be used for comparison of patient’s plasma levels was not detailed.

The analysis of nilotinib plasma levels is included in the statistics section in the revised manuscript.

Referee 2.
1. The precise definition of non-adherence, according to predefined criteria including persistence and execution is lacking. The criterium of 90 % compliance is not evidence-based and will not allow delineating the margin of non-adherence (‘forgiveness’), that actually needs to be determined: this is a major drawback (reference 1).

The authors agree with the reviewer that adherence should be considered as a continuous parameter. As a consequence, the objective, statistics and sample size calculation are reassessed and changed in the revised manuscript.

2. The patient reported outcomes will be assessed by a number of validated questionnaires but first a specific questionnaire assessing health related quality of life in CML patients (EORTC QLQ-CML24) is not used, and secondly the study protocol does not mention how these different questionnaires will be weighted. There will be considerable overlap and also contradictions. Its is not clear whether the questionnaires will be used comparatively. Therefore the study carries the risk of not being able to make an evidence-based selection between these questionnaires (reference 2).

At the time of study design, the EORTC QLQ-CML24 questionnaire was not yet available. We have considered using the general version i.e. EORTC QLQ-C30. However, considering
the chronic long-term condition of CML, we decided to use the SF-12 questionnaire. Since the study has already started and the first five patients are enrolled, we wish not to change the questionnaire. Concerning the reviewer’s concern on using the different questionnaires comparatively, we do not plan to compare the questionnaires, only to determine their influence on the efficacy of the treatment. We have clarified this in the revised manuscript.

3. The reasons for lack of response should be divided in BCR-related and BCR-unrelated. We have changed the primary efficacy end-point to the rate of MMR at 12 months.

4. The current guideline, evaluating the TKI-therapy at three months should be included. The guidelines are included in the manuscript.

5. The acronym MEMS also stands for: Medication Event Monitoring System. We agree with the reviewer that the acronym of MEMS should be Medication Event Monitoring System. We have changed this throughout the manuscript.

6. The pill count methodology includes unannounced interviews by phone: it is not mentioned at what time point and how frequent these will be planned. The fact that these interviews by phone will be unannounced should be mentioned in the informed consent (not included in the manuscript).

   We have included the time point of the telephonic pill count in the manuscript. Prior to the start of the study, patients are informed that they will be contacted at the end of the study period after 12 months. Patients are not informed about the exact content of this telephone call and the unannounced pill count, since this may influence the data. We do not wish to change this in the informed consent form.

7. Statistical review: In view of the need for better definition of non-adherence, as a continuous variable, the statistics need to be reassessed, including an expert statistician. The statistics are reassessed by the authors, of whom P.M. van de Ven is an expert statistician. As a consequence, the sample size had to be recalculated. The description of the statistics and sample size calculation are changed in the manuscript.

In view of the implementation of new Dutch CML treatment guidelines, nilotinib will possibly be less prescribed as first line treatment. Still nilotinib adherence remains an important issue and therefore we will amend the protocol to also include patients who are switched to nilotinib from another TKI because of resistance or intolerance. This has been changed throughout the revised manuscript.

Yours sincerely,

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