Author’s response to reviews

Title: Prospective Randomized, Double-blind, and Placebo-controlled Clinical Trial with Hydroxychloroquine (HCQ) in Patients with Inflammatory and Erosive Osteoarthritis (OA) of the Hands (Acronym: OA TREAT)

Authors:

Jacqueline Detert (jacqueline.detert@charite.de)
Pascal J Klaus (pascal.klaus@charite.de)
Joachim Listing (listing@drfz.de)
Vera Höhne-Zimmer (vera.hoehne-zimmer@charite.de)
Tanja Braun (tanja.braun@charite.de)
Siegfried Wassenberg (SWassenberg@clinic.de)
Rolf Rau (Rau.Herborn@t-online.de)
Frank Buttgereit (Frank.Buttgereit@charite.de)
Gerd R Burmester (Gerd.Burmester@charite.de)

Version: 3
Date: 6 August 2014

Author’s response to reviews: see over
Revised Manuscript: 2075461853123071 - Prospective Randomized, Double-blind, and Placebo-controlled Clinical Trial with Hydroxychloroquine (HCQ) in Patients with Inflammatory and Erosive Osteoarthritis (OA) of the Hands (Acronym: OA TREAT)

Dear editors, dear reviewers,

Thank you for reviewing our manuscript and thank you for the valuable comments and suggestions.

The following changes have been made in the revised manuscript:

- The title format has been changed to the official Trials format.
- The statement of ethical approval has been moved to the Methods section.
- The AUSCAN questionnaire is now discussed in detail in the Discussion section.
- Sample size paragraph: We now explain the basis of our sample size calculations in more detail. We explain that the sample size considerations are based on the EULAR recommendations for the planning of RCTs in patients with hand OA. These recommendations include review data on the efficacy of NSAIDs in hand OA patients. The authors of this paper provide pooled effect size (ES) estimates for pain and function which were used for the sample size calculations. However, pooled mean differences and standard deviations (SD) were not given. Nevertheless we now included SD estimates of AUSCAN pain and function change scores given by Grifka et al. a large RCT comparing lumiracoxib with placebo in more than 190 patients in each arm. Both specifications (ES and SD) allow the calculation of the corresponding mean differences (=ES*SD).
- The reviewer pointed out that an imbalance of the co-use of NSAIDs and/or analgesics might influence the outcome. We were aware of this problem and determined in the study protocol how to deal with a possible imbalance. Since the NSAIDs/analgesics use is associated with two opposing trends (new start/increased dosage likely in patients with higher pain on one hand and reduced pain in patients who used the drug on the other hand) we do not think that an adjustment with a co-variable is sufficient to control both effects. We determined that the co-use of NSAIDs and/or analgesics has to be investigated in detail and implications on the outcome have to be considered in
the interpretation of the AUSCAN findings for pain and hand function. Especially for the unlikely but most serious case that patients in the verum arm increase their dosage although the study drug seems to be effective we put down that a significant result has to be interpreted against the background of the imbalance of NSAIDs/analgesics use.

- We now explain the use of the multiple endpoint test in more detail. This test is an exact test keeping the type I error not only for normally distributed variables but also in a larger class of spherical and elliptically contoured distributions (Läuter et al. The Annals of Statistics 1998, Vol. 26, No. 5, 1972–1988). The key issue for the application is that all parameters included in the test are positively correlated. In a case in which a drug improved the pain intensity but deteriorated functional capacity this test would be inappropriate because of a low power. However, this case can be excluded.

- The format of the manuscript has been revised to appear more as a manuscript and less as a protocol.
- Limitations of the study have been included in the Discussion section.
- The references have been revised.

Thank you very much for considering the revised manuscript, we hope you will find it acceptable for publication in Trials.

Kind regards

P. Klaus on behalf of Dr. J. Detert et al.