Author's response to reviews

Title: Efficacy and safety of pamidronate in Modic type 1 changes: study protocol for a prospective, randomized, controlled clinical trial

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Author's response to reviews: see over
Please find below a point-by-point response to the concerns raised following the review of the original manuscript.

**Editorial’s request:** As requested, we have mentioned each author individually, which may of course lead to some redundancies. A few grammatical mistakes in English have moreover been corrected; we did not highlight them for the sake of easier reading.

**Reviewer’s report:**

1: We have stated that this is a phase 2 trial and the first RCT evaluating the efficacy of pamidronate in erosive degenerative disease, and have provided the hypothesis mostly in the Discussion section.

2: We have provided the requested information on the findings on Modic type 1 changes, and the fact that they represent a validated clinical finding, in the Background section. We have not, however, found any other classification criteria than the commonly described MRI features: type 1 (decreased signal on T1 and increased signal on T2), type 2 (increased signal on T1 and isointense or slightly hyperintense signal on T2), and type 3 (decreased signal on both T1 and T2). We did not include this well-known classification in the manuscript as we did not think it relevant in this context.

3: The dosage regimen used, 90 mg/day x two days, is mostly derived from our experience. It is based on the administration pattern sometimes found in the treatment of SAPHO syndrome, i.e. 180 mg over three days (60 mg/day). We considered the usual need for reducing length of stay and proposed a shorter administration pattern — the same total dose over only two days — with similar safety in our pilot study. For that reason, we have reused this regimen in the RCT.

4 (i): VIDAL is a French medical textbook containing summaries of product characteristics that are used as references. It states that pamidronate is used with no apparent increased adverse effect in patients with high serum creatinine, including those undergoing dialysis. However, it is not recommended to use it in the case of severe kidney failure, which is why we have listed “Contraindication to pamidronate (hypocalcaemia, **severe kidney**
failure or allergy)” among our exclusion criteria in Table 1 and included serum creatinine among the planned blood tests.

(ii): It is indeed implied that subjects should have an inflammatory back pain pattern. We have specified in the Inclusion Criteria presented in Table 1 that the pain should follow an inflammatory pattern, defined after review from recent literature on inflammatory back pain (1,2) and from inflammatory criteria of ankylosing spondylitis (3-7); an inflammatory back pain pattern was defined by the presence of at least one of three characteristics: waking at night because of pain, morning stiffness for longer than 60 minutes and maximal pain on morning.


5: We agree that the sample size calculation is accurate only if we assume that the SD of the difference (test vs. control) in change scores (initial vs. final) is the same as the previous SD of the change score found for treated patients in the open pilot study. Therefore, sample size estimation is based on previous works, which could be considered heterogeneous for the standard deviation of the change score. For example, in Poujol D, Ristori JM, Dubost JF, Soubrier M. Efficacy of pamidronate in erosive degenerative disk disease: A pilot study. Joint Bone Spine. 2007;74:663–4, the standard deviation of VAS was 19.1 at baseline, 22.7 at 3 months and 24.1 for change score. As standard deviation equals 30, our estimation appears near to the expected results and overestimates the value obtained in the pilot study. We think that, in light of these aspects, the sample size does not need to be larger.

6: We can confirm that the primary analysis will be VAS pain difference at three months using a Student’s t-test if normally distributed and a Mann–Whitney test if not. In a
second step, a multivariate situation should be proposed using a linear regression model to take adjustment factors into account. As was suggested by the reviewer, adjustments may threaten the randomized nature of the study. A random-effect model considering block as a random effect could also be proposed.

7: Failures at three months will indeed, irrespective of their group allocation, be offered the possibility of rescue treatment in the form of a dorsolumbar brace; its efficacy will be evaluated at six months, not to add a crossover component to this trial, but to ensure that the patient is at least partially relieved and to carry out the planned D180 evaluation.

8: As has been indicated in response six, a linear regression model will be proposed to consider adjustment on covariates. It is good practice to pre-specify covariates that will be used in adjusted analyzes for RCTs and not to select these based on screening but on statistical tests (CONSORT statement). The sentence on statistical methods has also been amended to clarify the adjustment considerations on analgesic use, treatments (and modifications) and other co-interventions during the study (e.g. physiotherapy). These aspects have been added to the revised manuscript.

9: As is indicated in the manuscript, the rate of subjects lost to follow-up at three and six months is considered to be minor. Therefore, we would like to clarify arguments to justify our choices from a clinical and statistical standpoint. Firstly, the visits at three and six months are common investigations in monitoring these patients in our hospital. Therefore, all patients should attend these visits and there is no risk of loss to follow-up for us. Secondly, if necessary, an appropriate imputation method may be considered. To assess the problem caused by missing longitudinal data, the estimation methods developed by Verbeke and Molenberg (8) will be considered. For other missing data, if the frequency of missing data is >5%, an additional analysis will be performed using the multiple imputation method (Stata software mi command (9)).


10 (i): This is indeed what we meant. The sentence has been changed accordingly in the revised manuscript.

(ii): See response 5. Sample size estimation was proposed in line with previous studies, which could be considered heterogeneous concerning the standard deviation of the change score. For example, in Poujol D, Ristori JM, Dubost JJ, Soubrier M. Efficacy of pamidronate in erosive degenerative disk disease: A pilot study. Joint Bone Spine. 2007;74:663–4, standard deviation of VAS was 19.1 at baseline, 22.7 at 3 months and 24.1 for change score. Fixing standard deviation at thirty points seems accurate and not underestimated according to the literature.
We agree with the reviewer’s comment but we had not taken into account multiplicity testing for the numerous secondary outcomes. Multiple statistical tests clearly increase the risk of type I error. The importance of this increase in risk, and whether adjustments should be made, seems far less clear (Imberger G et al. Plos One 2011). Published opinions vary enormously: some argue that any adjustment for multiplicity is entirely unnecessary (Rothman KJ. No adjustments are needed for multiple comparisons. Epidemiology 1990; Perneger TV. What’s wrong with Bonferroni adjustments. BMJ 1998), while others contend that adjustments should always be made when there is more than one test (Aickin M et al. Adjusting for multiple testing when reporting research results: the Bonferroni vs. Holm methods. Am J Public Health 1996; Gordi T et al. Simple solution to a common statistical problem: Interpreting multiple tests. Clin Ther 2004; Ottenbacher KJ. Quantitative evaluation of multiplicity in epidemiology and public health research. Am J Epidemiol 1998). Many suggest taking the middle ground, with various interpretations of when and how adjustments should be made (Bender R et al. Adjusting for multiple testing—when and how? J Clin Epidemiol 2001; Prochan MA et al. Practical guidelines for multiplicity testing in clinical trials. Control Clin Trials 2000). As most analyzes of secondary outcome parameters were exploratory and should have been underpowered, Feise et al. (BMC Med Res Methodol 2002) stated that we should consider whether a given study needs to be statistically analyzed at all and must be careful to focus not only on statistical significance (adjusted or not), but also on the quality of the research within the study and the magnitude of improvement.

This sentence was simply describing the follow-up analysis for included patients. It has been dropped from the revised manuscript.

The paragraph has been rewritten as requested in the Discussion section.

The manuscript follows CONSORT guidelines and Trials recommendations for study protocols as closely as possible.

The authors declare that they have no conflicts of interest and have given their written permission to publish this work.

The contents of the manuscript have not been published elsewhere. Correspondence should be addressed to:

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We hope that this manuscript will meet your requirements.
Sincerely

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