Reviewer's report

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

Version: 2 Date: 17 December 2013

Reviewer: Marissa Lassere

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Major compulsory revisions

1. State clearly that the trial is a phase 2 trial (as is noted in its information on ClinicalTrials.gov) and that there are no published controlled trials of pamidronate in erosive degenerative disease. I can find only one open study, the authors’ pilot study (ref 25). PLEASE STATE THAT THIS IS A PHASE 2 TRIAL IN THE ABSTRACT. Also please provide the hypothesis. I AM SORRY I WAS NOT CLEAR - PLEASE PROVIDE A HYPOTHESIS AT THE BEGINNING OF THE MANUSCRIPT i.e. IN THE INTRODUCTION OR THE METHODS. THE HYPOTHESIS SHOULD INDICATE THE CLINICAL POPULATION, THE INTERVENTION AND THE OUTCOME.

2. Describe the findings of Modic type 1 change and summarize the history that this is a validated clinical finding, especially in light of reference 1 which seems to pretty clearly show that Modic type 1 patients do not satisfy standard ankylosing spondylitis criteria. I presume the Modic 1 change marker is meant to confer a different prognosis compared to those without it. The typical reader (including many rheumatologists) will probably not be familiar with this information. I understand that Modic type 1 changes also occur in the normal population. Can this also be mentioned. The issue of course is that back pain is very common and Modic type 1 change is common therefore the two can coincide in the single subject. Are there published classification criteria? This is important regarding the generalisability of the trial results.

IS THERE A DISEASE CALLED EROSIVE DEGENERATIVE DISK DISEASE. MODIC’S 1988 PUBLICATION DOES NOT INCLUDE THIS TERM. MY UNDERSTANDING IS THAT TYPE 1 INDICATES MARROW OEDema, TYPE 2 POSSIBLY FAT REPLACEMENT AND TYPE 3 FIBROSIS. WHERE IS THERE DATA REGARDING THAT IT IS EROSIVE? PLEASE PROVIDE THE APPROPRIATE CITATION.

THERE IS LITERATURE THAT REFUTES THE CLINICAL CORRELATES OF MODIC TYPE 1 CHANGE AND BACK PAIN. THIS CONTROVERSY IS NOT REFLECTED IN THE MANUSCRIPT. MODIC IS A IMAGING BIOMARKER THAT HAS YET TO BE CONSIDERED A CLINICAL CONDITION.

"Moreover, patients with Modic type 1 changes usually experience acute flares of previous common chronic lower back pain, often with an inflammatory pattern, although mechanical
pattern characteristics can sometimes be found, hence a “mixed pattern”." This statement has no associated citation.

5. The sample size calculation is accurate only if one assumes the SD of the difference (test vs. control) of the change scores (initial vs. final) is the same as the historical SD of the change score found for treated patients in the open pilot study (ref25). This is unlikely given that this is a blinded study. Generally in blinded studies the difference scores are smaller but the SD may be larger. If so this will translate into a needed larger trial size. Furthermore the open label results were those seen at 6 months and not 3 months. NEVERTHELESS THE SAMPLE SIZE ANTICIPATES A 50% REDUCTION IN PAIN AND BLINDED STUDIES HAVE SMALLER EFFECTS WHICH MAY NOT BE CAPTURED BY THE SD. PLEASE COMMENT IN THE DISCUSSION.

6. There are an enormous number of statistical analyses planned. Can the authors confirm that the primary analysis is VAS pain difference at 3 months using a Student t test if normally distributed and Mann Whitney if not, without adjustment as any adjustments are discretionary. There are only 4 subjects per block on pamidronate and 4 on placebo. How are you going to use this in the analysis. Any differences may occur by chance and adjustments may threaten the randomised nature of the study? PLEASE INCLUDE YOUR RESPONSE IN THE DISCUSSION.

7. Can you clarify that failures at three months are provided a brace? How does efficacy of a brace at 6 months relevant to this trial of pamidronate efficacy? It is not at all clear from the protocol. It there a crossover component to this trial. THE EFFICACY OF THE RIGID BACK BRACE REMAINS UNCLEAR IN TERMS OF THE HYPOTHESIS AND THE ANALYSIS.

9. How will dropouts be analysed? THE ONLY RELEVANT ENDPOINT IS AT THREE MONTHS AS THIS IS THE PRIMARY ENDPOINT. THERE IS A DIFFERENCE BETWEEN MISSING VALUES THAT ARE DEALT WITH BY STATISTICAL IMPUTATION AND AND MISSING ENDPOINTS. ONE SOLUTION IS TO ASSIGN ALL MISSINGLE ENDPOINTS IN THE TREATMENT ARM THE WORST OUTCOME, AND ALL MISSING ENDPOINTS IN THE PLACEBO ARM, THE BEST OUTCOME. GIVEN THAT YOU ARE NOT EXPECTING MANY DROPOUTS THIS WOULD PROVIDE A ROBUST SENSITIVITY ANALYSIS.

10.

(iii) there are a great many secondary outcomes both as measures and the statistical tests that will be used. If all of them are assessed at 5% some will be significant by chance. Please comment. NEVERTHELESS GIVEN 48 PATIENTS AND 10 ADDITIONAL ENDPOINTS EACH AT THREE TIMEPOINTS, THE RISK OF A TYPE 1 ERROR IS HIGH AND MULTIPlicity IS AN ISSUE.

11. Could the manuscript be written so that it conforms to CONSORT guidelines. WHY DOES THE MANUSCRIPT NOT FOLLOW CONSORT/TRIALS GUIDELINES IN ALL ASPECTS?
Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
I declare that I have no competing interests