Reviewer's report

Title: Phase 1 safety and tolerability study of BMP-7 in symptomatic knee osteoarthritis.

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Reviewer: Xavier Chevalier

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The authors report a phase 1 placebo controlled dose ranging study on intra articular injection of BMP 7 in patients with symptomatic knee osteoarthritis (OA).

As tell in the introduction, we do need to explore new avenues in the treatment of knee OA and the intra articular route to administer molecules such as BMP-7 is in theory logical; therefore this kind of “pioneer” study should be encouraged.

However there a lot of limitations especially in the methods of this study which at least should be clarified.

The main criticism concerns the small number of patients per group, even if as tell by the authors the main goal was a safety and tolerability study. The efficacy results are secondary end points which should be interpreted with caution.

The second main criticism concerns the safety end points which are not made clear in the paper. What is the main end point in terms of safety? At which time ?.

It is very important after a local intra articular injecton to visit the patients at least in the 48 or 72 hours following this injection. Local AE after hyaluronic acid injections occurred mainly in the first 72 h following the injections. One concern is the possible local synovitis induced by this kind of molecules which could be clinically defined by a synovial fluid effusion plus an increase in the level of pain.

However the authors describe several side effects such as joint swelling, injection site pain, injection site swelling without clear definition of those AE. Thus, joint swelling should be recorded at day 2 by a senior physician during a physical examination and not only by just a telephone call. There is at least 3 patients: 2 in the 0.03 mg and 1 in the 1 mg group, who presented joint swelling but we don’t when it occurred (at which visit) and we have no idea of the intensity of this AE.

Otherwise the authors do not present any results from the laboratory and immunogenicity data: why? Which kind of tests have been performed?

There are a lot of caveats in the methods and in the presentation of results.

Page 5: inclusion criteria
Which dose of acetaminophen was authorized?

Page 6:
How was the first dose of BMP-7 chosen?
Page 7: test product and mode of administration could be easily reduced (there are repeated sentences)

Page 8: safety assessment: see previous remarks
Concomitant treatments: why acetaminophen was permitted in the 48 h before each visit? This could unmask the response.
How were the concomitant treatments collected?
There is no data reporting analgesics and NSAIDs consumption? Thus how could we be sure that there was no difference between groups?

Were the X rays performed in the same center and how the X rays were read?
The authors speak about MRI performed in some patients without presenting any results?

Page 9: results
Lack the following points which should be precised:
The exact description of the mean level of womac pain with SD in each sub group.
The Kellgren Lawrence classification or one other methods of radiological grading to be sure that there is no difference between groups.
The % of patients with bilateral knee OA in each group
The distribution of concomitant treatments in each group
The duration of knee OA
All these points are important to be sure that there is no difference at baseline between groups.

Some AE like lymphadenopathy in 2 patients receiving BMP-7 are intriguing. Could the authors comment?

The results section on efficacy are not interpretable and we suggest to be more cautious and to reduce this section; first the trial is not designed to look for efficacy; the number of patients is too small; The authors say in the discussion that there is no difference in terms of efficacy, but no statistical test are presented!

Moreover the results are really surprising: How the authors explain the low rate of placebo response at week 4 (12%) and then an increase effect at week 8 up to week 24 (which not in line with other reports on placebo response using the i.a route of administration). The results in BMP groups are divergent and the worst result observed with the highest dose is unexpected. Could the authors comment this result?

Similarly how the authors may explain a prolonged effect in BMP groups at week 24 owing the half life of this growth factor? Is it not purely a placebo effect?
Alternatively this study may include patients with a low level of pain at baseline.
It is very speculative as this study stands (follow up on osteophyte formation based on X Rays at 6 months) to tell that i.a of BMP-7 is safe in terms of the risk of bony formation; the authors should at least comment this potential risk of differentiation of local stem cells to an osteogenic lineage, under BMP-7 stimulation.

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.

**Declaration of competing interests:**

I declare that I have no competing