**(1)** My main concern is that there is insufficient evidence to support the conclusion “…M‑CSFRGD-HSA promotes bone remodeling and bone formation” or “M-CSFRGD-HSA inhibits bone resorption while allowing an uninterrupted bone formation process.”

The only bone formation outcome is PINP concentration in the circulation (Figure 4d). I think a reader would expect the claim of “increased bone formation” to be backed up by several techniques. Histomorphometry and dynamic histomorphometry could have provided direct evidence for the effect of M-CSFRGD-HSA on bone formation. Without any histological outcomes, the evidence for bone formation is weak.

If conducting more convincing experiments to determine osteoblast activity and bone formation is not a feasible option, I suggest that perhaps the results should be framed differently around the main findings of the study:

* The bispecific antagonist that was described in the previous publication was developed further, and its pharmacokinetic behavior was improved.
* M-CSFRGD-HSA had similar activity to M-CSFRGD in vitro (inhibition of osteoclast differentiation) and in vivo (preventing bone loss in OVX animals).

Bottom line: this is an excellent study if the aim was to improve the pharmacokinetic properties of the bispecific antagonist and investigate its bone effects. However, if the aim was to describe the mechanism of action of the bispecific antagonist, key experimental evidence is missing.

**(2)** I am not sure I understand the suggested mechanism of action of M-CSFRGD (or M-CSFRGD-HAS). The Results say: “To validate that the fusion to HSA did not affect activity of the proteins (i.e., inhibition of osteoclast differentiation)”; The Discussion: “The current study aimed to elucidate whether it is feasible to treat osteoporosis by dual targeting of c-FMS and αvβ3 integrin, i.e., inhibition of osteoclast resorptive function but not differentiation.”

Could you please clarify: are you suggesting that the bispecific antagonist either inhibits osteoclasts differentiation, activity, or both, but you don’t know and have not tested it here?

**(3)** Do you have a target journal in mind? The Results section includes quite a bit of experimental information and discussion. It reads very well, but some journals ask you not to include methods/ discussion in the Results. The Abstract would also need to be restructured according to the journal.

**(4)** The microCT results show that M-CSFRGD-HSA had a greater effect on %BV/TV and Tb.Th. at 2.5 mg/kg than at 10 mg/kg. Without testing the monospecific peptide at 2.5 mg/kg, it is inaccurate to say that the bispecific peptide is ‘superior.’ The two peptides appear similar at 10 mg/kg, and they might have also been similar at 2.5 mg/ml.

**(5)** Figure 1

* M-CSFRGD-HSA appears more potent than M-CSFRGD (greater inhibition in 50 and 250nM). Were these differences statistically significant? Perhaps you can test that.
* The Discussion says: “… inhibition of osteoclast resorptive function but not differentiation, thus preserving consecutive osteoblast-mediated bone formation process.” An experiment to determine osteoclast activity (for example, using bone slices to determine bone resorption pits) would help to support this suggested mechanism.

-Please also note that panel (a) in Figure 4 is cropped and the coloring in inconsistent in panel (d)**.**