Reviewer’s report

Title: Boronic Prodrug of 4-Hydroxytamoxifen is More Efficacious than Tamoxifen with Enhanced Bioavailability Independent of CYP2D6 Status

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Reviewer: Hitoshi Zembutsu

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In this manuscript, authors showed that ZB497 effectively delivers a markedly increased plasma concentration of 4-OHT in mice and the boronic prodrug have far superior bioavailability compared to tamoxifen or 4-OHT as measured by the area under the plasma concentration time curve (AUC) using mouse model. However, the below critical issues were observed in this manuscript.

Major comments,

1. In result section (pp. 10-11), authors said that “While tamoxifen administration did not yield quantifiable endoxifen levels, 4-OHT orally given to mice generated an endoxifen concentration comparable to 4-OHT, with an AUC value of 61.2 ng/mL*h”. However, endoxifen has been known to reach greater than 6-fold higher plasma concentrations than 4-OH tamoxifen in human taking tamoxifen. If this discordance is due to the difference of species, the mouse model itself is not appropriate for this PK study.

2. In figure 4, 4 tumor growth curves (2 kinds of doses for tamoxifen and ZB497, respectively) except control looks similar. Was statistically significant difference observed between them?

3. In figure 4, authors need to verify this results using several breast cancer cell lines.

4. Although I do not know how the authors calculated, the following description in discussion section (p. 15) is inappropriate. This should be deleted.

“While it is difficult to make a direct comparison between human and mouse dose responses, it should be pointed out that the human dose for tamoxifen varies between 20 and 30 mg/day, which depending on patient weight would be in the range of 0.2-0.3 mg/kg. Thus, the 1 mg/kg dose we used would roughly correspond to 3-5 times the standard human dose.”

Level of interest: An article of insufficient interest to warrant publication in a scientific/medical journal

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 interests