Author’s response to reviews

Title: Identification of cryptolepine metabolites in rat and human hepatocytes and metabolism and pharmacokinetics of cryptolepine in Sprague Dawley rats

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RESPONSE TO REVIEWER COMMENTS

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REVIEWER 3

Comment 1: The sex of the cryopreserved hepatocytes from humans and rats should be listed. The authors should also indicate if these were pooled or single donor samples.
Response: A pool of mixed gender cryopreserved hepatocytes from humans and rats were used for the in vitro metabolite profiling. This has been classified in the manuscript (Page 4 line 14)

Comment 2: Page 4 line 35: List the final concentration of DMSO in metabolite profiling experiments.
Response: The final concentration of DMSO in the metabolite profiling experiments was always less than 0.1%. A sentence clarifying this has been added to the manuscript (Page 4 line 38).

Comment 3: Page 5, line 28: Harlan Laboratories is now Envigo.
Response: Name change has been effected (Page 5 line 26)

Comment 4: Page 5: Intravenous drug administration through which vein (jugular, tail vein etc). Also which vein for blood sampling.
Response: Intravenous drug administration was via a catheter in the left jugular vein whereas sampling was via a catheter in the right jugular vein (Page 5 line 44 and 52).

Comment 5: Please clarify how bioavailability was calculated for animals 3 and 4. There was no iv data from these animals to make this calculation. Bioavailability could be calculated from the pooled data from both animals for each administration route.
Response: The oral bioavailability of animals 3 and 4 were calculated using the formula:
AUCoral* i.v. Dose/ AUCiv* oral Dose.

Oral bioavailability values were calculated using individual AUCpo values and the average AUCiv. The fraction obtained was multiplied by 100 to obtain the F% (oral bioavailability) indicated in Table 3.

Comment 6: The X-axis should be truncated for Figures 4 and 5. This would allow the reader to better evaluate the profiles. It also appears that the compound undergoes biliary recycling based on the profiles, but this was not mentioned in the results or discussion.

Response: The x-axis of Figures 4 and 5 have been truncated. Cryptolepine has been shown to undergo hepatobiliary circulation (Reference 13 and 14) however, due to the metabolism focus of this paper, the low PK sample size and the variability of the data, extensive discussion of the PK parameters was omitted.