Reviewer’s report

Title: Phase I Study of TP300 in Patients with Advanced Solid Tumors with Pharmacokinetic, Pharmacogenetic and Pharmacodynamic Analyses

Version: 2 Date: 25 March 2012

Reviewer: Laurent Rivory

Reviewer’s report:

Major Compulsory

1. The pharmacokinetics of the parent drug TP300 are surprisingly not provided in any form and the fact that both TP3011 and TP3076 will be present as a mixture of lactone and carboxylate forms appears to have been overlooked.

2. Page 5. The authors propose that a reduction in PK would reduce the likelihood of diarrhoea as a side effect of therapy (e.g., “be less inter-individual variation in activation and toxicity with TP300 than with irinotecan; specifically, it would be expected that severe diarrhea should not be an issue”). There is no basis for such a concept as the underlying cellular mechanisms and distribution are what determines the target organs, not variability.

3. Page 6. A proposed major finding is that “variability was small”, but this is not quantitated or defined.

4. Page 6 and elsewhere. The linearity of TP3076 and TP3011 PK was not assessed formally and the data appear to indicate non-linearity at the 8-12 mg/m2 range.

5. Page 7 and elsewhere. The modelling of haematological toxicity with exposure is said to be “strong”, but no statistics (e.g., R2) are provided.

6. Page 8. The Comet data are said to indicate a trend although there was no clear relationship/ “Although there was no clear relationship between TP300 dose and the extent of strand breaks, there was a trend towards higher doses being associated with greater DNA damage”. There is no evident trend from eye-ball ing the data and if not significant, then any “trend” is in any case meaningless.

7. Page 8 and elsewhere. It is claimed that TP3076 is rapidly converted, but no kinetic data are presented. For example, on page 9, it is claimed that “Pharmacokinetic data confirm that TP300 is rapidly converted in plasma to the active metabolite TP3076”.

8. Page 8. It is claimed that “Target interaction with the induction of DNA strand breaks was shown”, but the Comet data are inconclusive and there is no data shown of topoisomerase I inhibition.

9. Page 9. Glucuronidated TP3076 was not detected, but it is not clear what attempts were made to detect it. Furthermore, the statement “reflecting UGT1A1 variant status had no influence on exposure to either TP3076 or TP3011” is somewhat of a non-sequitur as glucuronidation of TP3011 was not investigated.
10. Page 9. It is claimed that “TP300 has advantages over other agents in this class in terms of tolerability and the predictability of its principle toxicity, myelosuppression”, but this has not been formally assessed. Although the comparison with CPT-11 is interesting, I would have expected Topotecan to be the more appropriate drug for comparing profiles.

11. Page 11. Exclusion criteria included “prior cytotoxic chemotherapy” which is not consistent with the fact that several patients had previously been treated with CPT-11.

12. Page 11. I am concerned that the details regarding the infusion medium are not provided. TP300 is said to spontaneously convert to TP3076 at pH>5. Most infusion solutions are not buffered but some are, so the pH of the drug infusion solution will depend on the formulation of TP300 and the dose of TP300 (ie if TP300 formulation is acidic, then increased dose in a fixed infusion volume will cause a reduction in pH). Furthermore, and in the absence of more details on TP300, the motivation for using TP300 is not evident if it is required to be maintained at pH<5, as this is a limitation also with the conventional 20(S)OH camptothecins.

13. Page 12. Where was blood drawn from? What was the extraction method? What was the analytical method? Were samples acidified so as to measure total TP3011 and TP3076 or were only the lactone forms assayed? The methodology is insufficiently described.

14. Page 12. Some of the data points in Figure 2 are below the limit of quantification.

Minor

15. Page 5. I think that UGT1A1 can also form acyl and N-glucuronides, so “lacks the phenolic-OH group required for glucuronidation” is not strictly correct.

16. Page 6 and elsewhere. TP300 PK should be shown in Figure 2.

17. Page 8. It is not just the side-chain of CPT-11 that accounts for its acetylcholinesterase inhibition, so “the side chain present in CPT-11 that has acetylcholine esterase activity being absent” should be rephrased.

18. Page 9. “as acute cholinergic reactions are associated with the piperidine moiety of irinotecan, not found in TP300” should be referenced.

19. Page 9. “Hepatic aldehyde oxidase converts TP3076 to a further metabolite TP3011” should be referenced.

20. Page 12. What were the two animal species tested?

21. Page 13. Was the urinary ratio adjusted for the molecular weight difference between the parent drug and the metabolites?

22. Page 13. The PCR method needs to be referenced or details provided.

Other

23. Page 4. “TP300 has activity in the nanomolar level across a range of tumour types” could be rephrased.
24. Page 4. Need to accord plural in “TP3011 and TP3076 are equipotent as Topo-1 inhibitors, with an IC50 in the”
25. Page 6. Punctuation needs to be fixed in “lasting between 1.5-5 months; Five”.
26. Page 11: Punctuation needs to be fixed in “Standard Phase I trial exclusion criteria included, exposure..”
28. References: #7 – United misspelt. #8, #17 – page numbers missing.

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

I declare that I have no competing interests