

Protocol 0107—488

PI: R.R. MacGregor

Title: A Phase 1a, randomized study of escalating single doses of VRX496 in subjects with AIDS

### **Study Design:**

1. Comment and questions regarding study aim 1:

Although a dose escalation study is the usual proper design for determination of the relationship between drug dose and toxicity, it is not clear that this accomplishes the safety purposes need in this phase I clinical evaluation of a lentivirus vector. Admittedly, the study drug is the VRX496-transduced CD4 cells and so advancing the doses of this drug is conventional, but it is recognized that the infusion of CD4 cells, at the doses proposed, is not usually toxic. The toxicity that is most important to determine, however, is that potentially contributed by the lentivirus vector. This is likely to take longer to observe than the planned interval of 28 days between doses. Thus, it is not clear why this study design was chosen.

1. Please indicate how this dose escalation study design adequately addresses specific aim 1.
2. What are the dose escalation rules? Dose reduction guidelines? Stopping rules?
3. Justify  $n = 3$  in the dosing level cohorts?
4. Justify why there is no upper limit to the HIV load, without which the study population could be so heterogeneous that it could affect observations of toxicity.

2. Comment and questions regarding study aim 2:

The endpoints chosen for this aim are virus load reduction and CD4 count stability, and the assumption is that the transduced CD4 cells will survive infection and contribute to this end. Surely the risk/benefit assessment suggests some potential for the genetic transfer to influence CD4 survival.

- a. Please justify the choice of these derived endpoints, rather than a direct observation of transduced cell survival.
- b. Why was a vector control-transduced CD4 not included in this study?
- c. What is meant by PK studies of plasma VRX496 during the first 72 hours?
- d. What type of and what is the purpose of the ELISPOT assay?

3. Comment and question on choice of vector:

Although consideration of homology minimization has been important in vector design, there is still homology in the LTR regions.

- a. Is the VRX496 lentivirus vector safer than a lentivirus vector in which the LTRs have been replaced with another promoter?
- b. Is there data to support the theoretical concept that the introduction of codon degeneration and the synthetic poly A signals decrease recombination events between vector and helper virus?
- c. Why should this vector be the first lentivirus to be used clinically when there is potential to further refine it with modifications that would reduce homology with helper virus?

### **Pre-Clinical Studies:**

4. Have the helper and vector plasmid DNAs been sequenced? Where are these DNAs produced?
5. There is data that the effect of freeze/thaw does not significantly effect CD4 expansion. How many HIV-1 patient derived CD4 specimens have been observed to support this point?
6. There is breakthrough wt-HIV from transduced CD4 cells in culture by day 13 (Fig 14), at a time when transduced cells frequency is predominating (Fig 15). Is this from the untransduced population or does this wt-HIV virus have a modified ENV?
7. Regarding anti-HIV effect in vitro, is there any inhibitory effect when HIV2 strains are used to challenge the transduced cells.
8. On page 19, it is stated that the investigators have systematically examined the types of recombination events that could occur between VRX496 and wt-HIV, and show on theoretical grounds that “it would not be possible for recombination to arise between VRX496 and wt-HIV.” On what empirical data is this statement based? For example, if the vector were to package VSV RNA could this become integrated DNA and lead to unexpected events? Could there be non-homologous recombination? What data supports your anticipation of no such possible recombination events?
9. It seems to be true, but because of its importance to the Committee’s review, what is the basis for stating that CD4 leukemias harboring HIV have never been described?
10. What is the justification for relying on the SCID murine model for assessment of potential tissue distribution?

### **Clinical Protocol:**

11. Consenting procedure. Would this study not benefit from a “patient advocate” to assist both the PI and the participant?

12. Confidentiality. What measures will be in place to assure confidentiality of the participants in this “high-profile” study?
13. There is a discrepancy (6 wks vs 28 days) between the Points to Consider document and the clinical protocol in regard to the interval between dose level escalation. Which is correct? If 28 days, will this be sufficient to achieve all necessary observations for aim 1, especially evidence for vector recombination?
14. How long will HAART be withheld during participation in this study? Is this ethical?
15. Regarding inclusion criteria, should not adequacy of venous access be a requirement?
16. The consent indicates that the study duration is 6 months and should it not mention that annual follow-up will be requested for life?
17. Will there be an independent data safety monitoring board for this study?

#### Other Concerns

Please clarify whether Dr. Carl June is an investigator on this study and if/how conflict of interest in regard to the CD4 expansion needs/will be managed.