

Reply to Dr King's comments our Protocol #01-07-488 "A phase 1 open label clinical trial of the safety and tolerability of single escalating doses of autologous T cells transduced with VRX496 in HIV positive patients."

First, the principal investigator, co-investigator and sponsor-investigator would like to thank Dr King for her questions and comments. Certainly, the protocol and consent form needed some extra work and so we appreciate her guidance. The protocol and consent forms are much stronger documents because of her constructive questions and comments.

Dr King's first question relates to inconsistencies between patient selection in the protocol and the consent form. We have now corrected & clarified these. Our initial goal in describing the target patient-subject cohort was to select a patient-subject population that has no good antiviral drug options left. The patient-subject population that has been selected are those that have discontinued or failing (in contrast to the previous used term, failed) antiretroviral drug therapy (including HAART) as shown by a viral load of >500 copies per ul plasma for at least 6 months. In the case that the patient-subject is failing antiretroviral therapy, he/she may enroll in the study and continue the same antiretroviral regimen for whatever ongoing benefit it might bring. The patient-subject would need to consent to stay on this regimen for the duration of the study (6 months). Therefore, the patient-subject may be enrolled in the study and yet continue on his/her existing antiretroviral regimen as long as the existing regimen is failing, as shown by a viral load of >500 copies per ul plasma. This has now been clarified in the consent form in the invitation to participate section.

Dr King had some concerns about the limitations of participating in a phase I study and how this information is transmitted to patient-subjects. We have now included language in the benefits section to reflect the safety nature of the study (see consent form, attached).

Dr King's second question refers to dose escalation design. The 1.0×10^9 initial dose level was selected because it is the lowest dose at which VRX496 modified cells could be detected in the blood after their infusion & biodistribution, and thus is the minimal dose at which some sort of benefit could be expected. It is possible that if these modified cells have a selective advantage for survival over endogenous T cells, then over time, the expanded population of modified cells could provide some tangible benefit to the patient. At higher doses, the tangible benefit may be seen sooner and more significantly than at lower doses. Therefore, we cannot say for certain that there will be no benefit for the patient even at the lowest T cell infusion dose.

It also follows that we cannot say for certain that there will be any benefit for the patient even at the highest T cell infusion dose. The benefit section of the consent document accurately reflects the lack of expectations for the study.

In reference to question 2 about the harm-benefit balance for each dose I will make some general comments. We can say that as the dose of VRX496 modified cells increases, so does the potential beneficial anti-HIV effects. However, as the dose of T cells is increased, so does the risk for wt-HIV replication, particularly in cells that sub-optimally contain VRX496 or may not contain VRX496 at all. Clinical studies have suggested that the viral load can increase in HIV-infected patient-subjects that are infused with cells that are not modified to resist HIV-infection. Therefore, similar effects may be seen in this study for a potentially subset of cells that are not optimally transduced with vector. However, our release testing criteria will ensure sufficient transduction of the cells, so an adverse increase in viral load is not expected to occur in the proposed study.

In reference to question 3, we are now instituting a DSMB for this study.

In reference to question 4, Dr King's comments were the only one received in time for this written review. I will provide additional comments, as they relate to the other reviewer's remarks, for the September 6th meeting.

In reference to question 5, patient has been replaced with patient-subject in the protocol. The word "investigation treatment" has been replaced with "experimental treatment."

The purpose section has been modified so as not to overstate the potential benefits of the study. If the wording remains problematic, we would be delighted if Dr King can help us with suitable wording.

In reference to defining VRX496, we have now modified the description sentence to state: "VRX496 is an anti-HIV gene transfer product." It would be difficult to provide further technical information that would be useful to the patient-subject. However, we are willing to explore this to further modify the wording if Dr King feels that this is critical.

In reference to germ line transmission of VRX496. Germ line transmission of VRX496 is unlikely since the infused product are VRX496 modified cells, and not a vector product. Additional vector associated risk information is now provided in the Risk section of the consent form.

In reference to the comment referring to the vague and overoptimistic benefits section: We believe we have addressed this issue in the modification to the text described above and in the revised consent form (attached). If the wording remains problematic, we would be delighted if Dr King can help us with suitable wording.

Finally, we would again like to thank the reviewer for the constructive and well thought out questions and comments.

Thank you for the opportunity to present our protocol for review.

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