

## SCIENTIFIC ABSTRACT

The proposed study is a Phase I/II, open-label, single center, multiple dose trial to evaluate the safety and efficacy of an HIV-based lentiviral vector (VRX496) carrying an antisense sequence targeted to HIV for the treatment of HIV infection. The primary objective of this Phase I/II study is to determine the safety and tolerability of multiple doses of autologous VRX-496-transduced CD4+ T Cells. Secondary objectives are to assess the persistence and trafficking of the vector *in vivo* and the efficacy of multiple doses.

Safety will be assessed by monitoring adverse events, performing blood chemistries and hematological analyses, by urinalysis, by virological assays (plasma HIV-viral load) and by physical examination. In addition, patients will be monitored routinely for the presence of replication competent lentivirus (RCL). Trafficking and persistence of VRX496 cells will be assessed by rectal biopsy.

VRX496 is a completely gutted lentiviral vector and does not code for any viral proteins. The viral vector contains an antisense sequence targeted to the HIV envelope (*env*) gene. VRX496 directly interferes with wild-type HIV (wt-HIV) expression via anti-*env* antisense expression in vector transduced CD4 cells that become infected with wt-HIV. Expression of the anti-HIV antisense *env* from a HIV vector transcript would target wt-HIV RNA and destroy it, and hence, decrease productive HIV replication from CD4 T cells. The clinical goal for this treatment approach, therefore, is to improve immune function.

Data from *in vitro* studies have suggested that HIV vectors such as VRX496 could potentially reduce viral loads in HIV-infected individuals and thus could delay the onset to AIDS while promoting CD4 T cell survival and providing the immune system with a better chance to control the infection. Additionally, results from experiments in SCID mice (mice with transplanted human immune cells) indicated that the human cells transduced with VRX496 and implanted into the SCID mice do not elicit any overt adverse effects.

Results to date in the Phase I clinical study (University of Pennsylvania Protocol #704671) in which HIV-infected patients have been administered a single autologous infusion of VRX496-transduced CD4+ T cells have shown that the infusion has been well tolerated and safe, that the vector has persisted *in vivo*, and that there have been trends in viral load reduction from pre-dose levels while CD4 T cell numbers have remained stable. Please refer to Addendum 1 and the background section of the protocol for clinical summaries of the first four patients treated in the Phase I trial.

In this planned Phase I/II multiple dose study, up to 25 HIV-infected patients will be enrolled at the University of Pennsylvania. Patients eligible to participate in the trial will be males and females  $\geq 18$  years of age who are responding to highly active anti-retroviral therapy (HAART) regimen and have CD4 T cell counts of  $\geq 200/\text{mm}^3$  and viral load  $\leq 50$  copies per ml. Patients will undergo up to 2 leukapheresis procedures with subsequent CD4 T cell isolation. Patient CD4 T cells will be transduced *ex vivo* with the vector, expanded for 8-11 days, and then the modified cells will be reintroduced into the patient. Each subject will receive up to 2 cycles of 4 doses each. Each infusion will be given biweekly and consist of approximately  $10^{10}$  cells suspended in 100 ml; infusions will be given over approximately 10 minutes. Subjects will be examined weekly during the treatment phase. To assess antiviral efficacy, patients will undergo structured treatment interruption 2 weeks following the last infusion, and the time to viral recrudescence and the viral set point monitored at twice weekly intervals. HAART will be reinstated when viral load is  $\geq 20,000$  copies/ml. Follow-up examinations will be conducted at approximately monthly intervals up to 6 months, thereafter; long term follow-up will be performed annually for 15 years.