

### SCIENTIFIC ABSTRACT

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

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 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 for clinical summaries of the first three patients treated in the Phase I trial.

In this planned Phase I/II multiple dose study, up to 30 HIV-infected patients will be enrolled in up to 4 clinical sites. Patients eligible to participate in the trial will be males and females  $\geq 18$  years of age who have failed at least one highly active anti-retroviral therapy (HAART) regimen and have CD4 T cell counts of  $\geq 150/\text{mm}^3$  and viral load  $\geq 1,000$  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 100 ml of  $10^{10}$  cells infused over approximately 10 minutes. Subjects will be examined weekly during the treatment phase. 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.