M-I-A (2). SCIENTIFIC ABSTRACT

The proposed study is a Phase 2, open-label, single center 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 study is to determine the safety and tolerability of two infusions of autologous VRX-496-transduced CD4+ T Cells. Secondary objectives are to assess the persistence of the vector in vivo, and to evaluate improvements in immune function and antiviral effect of VRX-496-transduced CD4+ T cells.

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.

In a Phase 1 study five highly treatment-experienced; HIV-1-positive subjects with virologic failure each received an infusion of 0.6-1.0 x 10^{10} VRX496-transduced CD4+ T cells. The single IV infusion of gene-modified autologous CD4 T cells was well tolerated in all 5 patients. Viral load was stable and one subject exhibited a sustained decrease in viral load. CD4 counts remained steady or increased in 4 subjects and sustained gene transfer was observed two years after infusion in two subjects. Self-limiting mobilization of vector was observed in 4 out of 5 subjects. There was no evidence of insertional mutagenesis after 21-36 months. Immune function improved in four subjects. No hematological or neurological abnormalities have been observed and no new malignancies have been noted.

In an ongoing Phase 2 study evaluating the safety and therapeutic effect of single and repeated doses of VRX496-transduced CD4+ T cells in HIV-1-positive subjects failing one or more ART regimens, 39 subjects have been enrolled (13 subjects received 4 infusions and 11 subjects received 8 infusions of 0.5-1.0 x 10^{10} cells/infusion). An additional fifteen subjects received a single bolus infusion of 10, 20, or 30 billion transduced CD4+ T cells (up to 5 subjects per group). To date, the infusions have been well tolerated. There have been no dose-limiting toxicities and no abnormalities in hematologic testing

In this planned Phase 2 study, up to 20 HIV-infected patients will be enrolled in a single clinical site. Patients eligible to participate in the trial will be males and females ≥18 years of age who have not previously taken failed antiretroviral therapy and have CD4+ T cell counts of ≥ 500/mm^3 and viral load ≥ 5,000 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 2 infusions provided at 9 month intervals. Infusion consisting of 100 ml of 10^{10} cells will be infused over approximately 10 minutes. Subjects will be examined monthly for 9 months following each infusion. Long term follow-up consists of semi-annual evaluations for the first 5 years, followed by annual check up for the next 10 years.