

M-I-A (2). SCIENTIFIC ABSTRACT

The current protocol is a rollover study for subjects who completed the main study (protocol VRX496-05-002). The study will evaluate the effect of re-infusing a single bolus of VRX496 transduced T cells in subjects who met defined protocol criteria in the main study. Approximately 30 subjects may be eligible to receive another infusion of 10 billion modified cell at approximately 9 to 12 months after receiving their last infusion in the main trial. The primary objective of this study is to determine the safety and tolerability of re-infusion with 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). Long term follow-up will be performed semi-annually for the first four years followed by annual check ups for the next ten years.

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. Re-infusion with VRX496 is not expected to cause any safety concerns.

The main study (VRX496-USA-05-002) is currently ongoing for subjects receiving the single bolus infusions. Single or repeated Infusions have been well tolerated and there have been no dose-limiting toxicities and no abnormalities in hematologic testing

In the ongoing single bolus cohorts, preliminary results indicate some beneficial effect on viral load and CD4 counts. Viral load nadir was observed at approximately 3 months after infusion for 13 subjects. The decline of viral load from baseline ranged from -1.74 log to -0.48 log, with a median decrease of -0.3 log. This effect, however was not sustained and viral load tended to return to baseline values. These data are encouraging, especially in view of the fact that 14 out of 15 subjects are not on any background antiretroviral drug therapy. Under these conditions viral load is expected to either increase or remain stable. At the current time, nine out of fifteen subjects have shown an increase in CD4% (mean increase, 3%; range 1% to 6%). Of the seven subjects who have completed the 6-months post infusion visit, five subjects have a mean CD4 counts increase relative to baseline of 32% (range 8% to 62%) and viral load is below baseline in 2 subject (-1.93 and -0.58 log) and unchanged from baseline in the other 5 subjects.

During the process of cell manufacturing, purified CD4+ cells derived from the subject's apheresed product are transduced with the VRX496 vector and expanded ex-vivo by using anti-CD3/CD28 beads as artificial antigen presenting cells. From a typical starting material of 2 billion purified CD4+ cells, the final yield after expansion is of the order of 80 billion cells. Therefore, for subjects in the VRX496 USA-05-002 trial that were enrolled in the 4-dose cohort and the single infusion cohorts, additional cell doses that were not used initially were kept viably frozen for future infusions. In view of the possibility that there may be some therapeutic effect with VRX496, and no safety concerns have been raised, the risk-benefit ratio favors intervention with a second infusion of the product.