Background: The E. coli-derived MazF endoribonuclease specifically cleaves single stranded RNAs at ACA sequences. HIV-1 contains over 240 ACA sequences, making it especially sensitive to MazF activity. In this study, autologous CD4+ T cells are modified using a retroviral vector containing the mazF gene expressed under the control of the HIV LTR. MazF expression is thus activated by Tat conditionally during HIV replication. This study is designed to evaluate the safety and durability of MazF-modified CD4+ T (MazF-T) cells, and assess related antiviral effects.

Methodology: This is an exploratory Phase I, Open Label, Dual Cohort study evaluating safety, tolerability and immunogenicity of autologous CD4+ T cells expressing the MazF endoribonuclease gene in HIV+ subjects. Both cohorts consist of subjects on combination antiretroviral therapy (cART) with undetectable HIV-1 RNA levels and with CD4 counts >350 cells/mm³ in Cohort 1 and >450 cells/mm³ in Cohort 2. Subjects in cohort 1 remain on cART throughout the duration of the study. Subjects in cohort 2 participate in a 16 week analytical treatment interruption (ATI) beginning 2 weeks post T cell infusion. Subjects in cohort 1 participate in an analytical treatment interruption lasting a maximum of 16 weeks.

Results: To date, all 6 subjects in Cohort 1 have each received a single infusion of 0.5-1x10^6 cells. All 10 AEs related to study drug have been grade 1 in severity. Based on available data, 3 of 6 subjects had an increase in CD4 count and effects on HIV viral load.

Safety- Cohort 1
- To date, all Cohort 1 subjects (N=6) have been infused. Each subject received a single infusion of 0.5-1x10^6 MazF-T cells.
- There has been 1 SAE, probably related to MazF-T. This event was a self-limited cytokine release syndrome which resolved within 48 hours.
- All 10 AEs related to study drug have been grade 1 in severity.
- Since subjects were on continuous cART, viral loads remained undetectable throughout the study.

Conclusion
Preliminary results suggest that autologous MazF-modified CD4+ T cells are safe and well-tolerated in aviremic HIV+ subjects and that MazF-T are able to persist at least 6 months post-infusion. Future results from Cohort 2, in which subjects participate in an analytical treatment interruption, are expected to further elucidate the anti-HIV effects associated with MazF-T cells in the presence of active HIV replication.

Funding Source: Takara Bio Inc., http://www.takara-bio.com