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BIT225, a Novel Inhibitor of HIV-1 Release from HIV-1 Reservoirs of the Myeloid Lineage

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Background: Biotron Limited's lead compound, BIT225, blocks Vpu ion channel activity and has anti-HIV-1 activity *in vitro*. The antiviral effect is greater in cells of the monocyte lineage; with circulating monocytes able to differentiate into tissue resident macrophages, a key cellular reservoir of HIV-1. BIT225 is a novel antiviral drug that disrupts viral assembly within the host cell, resulting in a substantial loss of infectivity of the progeny virus. BIT225 was found to be well tolerated in a Phase I clinical trial in healthy volunteers. This study is the first clinical evaluation of BIT225 therapy in HIV-1 infected subjects.

Methods: BIT004 is a phase 1b/2a, placebo-controlled, randomized study of the safety, pharmacokinetics and antiviral activity of BIT225 in 21 HIV-1$^+$, antiretroviral therapy naïve subjects. Subjects received BIT225 (400 mg BID) or placebo treatment for 10 days (randomized 2:1). Twenty-one subjects were enrolled and completed treatment. To explore the potential of BIT225 to reduce the viral burden within the monocyte reservoir, CD14$^+$ monocytes isolated from the peripheral blood on days 0, 5, 10 and 20, were cocultured *ex vivo* with MT4 T cells. *De novo* HIV-1 replication was measured by p24 activity of released virus into the culture supernatant to day 25 of coculture. In addition, monocyte samples were collected for RT-PCR HIV-1 single copy assay analysis.

Results: Cocultures were established with monocytes isolated at days 0, 5, 10 and 20 for both BIT225 treated and placebo controls. Placebo controls demonstrated similar levels of infectious virus released from the monocytes, at all time points, indicative of a stable level of infection. BIT225 treatment resulted in a reduced level of HIV-1 transmission from this compartment. When the BIT225 treated patients were grouped at baseline into those with high versus low viral load (using the median), BIT225 resulted in a significant reduction in the amount of infectious virus released from the monocytes in the higher viral load cohort.

Conclusions: This study's unique design demonstrates that BIT225 can significantly reduce the dissemination of HIV-1 from infected monocytes. Potentially this has important ramifications for diminishing the seeding/re-seeding of the viral reservoir.