

AMD-3100 CXCR4 Receptor Blocker Fails to Reduce HIV Viral Load by ≥ 1 Log following 10-Day Continuous Infusion

C. Hendrix*¹, A. C. Collier², M. Lederman³, R. Pollard⁴, S. Brown⁵, M. Glesby⁶, C. Flexner¹, G. Bridger⁷, K. Badel⁷, R. MacFarland⁷, G. Henson⁷, and G. Calandra⁷ for the AMD-3100 HIV Study Group

¹Johns Hopkins Univ., Baltimore, MD; ²Univ. of Washington, Seattle; ³Case Western Reserve Univ., Cleveland, OH; ⁴Univ. of Texas Med. Branch, Galveston; ⁵AIDS Res. Alliance, West Hollywood, CA; ⁶Cornell Univ., New York, NY; and ⁷AnorMED, Langley, BC, Canada

Background: AMD-3100 is a CXCR4 receptor blocker with anti-HIV activity; it was well tolerated in single-dose volunteer clinical studies of up to the highest dose of 80 mug/kg. The objective was to test the safety, pharmacokinetics (PK), and antiviral effect of AMD-3100 administered for 10 consecutive days by continuous intravenous infusion in an open-label, dose escalation study.

Methods: 40 HIV-infected patients with viral load >5000 copies/mL, on no or stable antiretroviral regimens were enrolled. Contingent on pre-defined toxicity limits, the dose was escalated from 2.5 mug/kg/hr up to 160 mug/kg/hr. SI phenotype was required in higher dose cohorts.

Results: Most subjects were black (55%), male (98%), and on no ARV therapy. HIV phenotype was SI (28%), NSI (45%), or not tested (17%). Adverse experiences were generally common with gastrointestinal side effects most common. 1 patient (5 mug/kg/hr) had thrombocytopenia, which was serious and drug-related. 2 patients (40 and 160 mug/kg/hr) had unexpected, not serious adverse events of PVC's. A total of 3 patients discontinued the study drug due to drug-related adverse events. Some patients in all cohorts had atrial tachycardia. Most patients in the 80 and 160 mug/kg/hr cohorts had paresthesias. PK analysis (n=25) showed dose proportionality for AUC and Cmax across dose cohorts. In the highest dose cohort (160 mug/kg/hr; n=2) the Cmax range was 3300-3540 ng/mL. No SI patient had a 1-log drop in viral RNA, the predetermined criteria for activity. 1 SI patient (160 mug/kg/hr) had a 0.9 log drop at day 10 (1.4-log drop at day 18). 4 other patients, NSI (3) or undetermined (1), had a viral load change of >0.5 log, but this was thought more likely due to concomitant anti-HIV drugs or other factors.

Conclusion: We failed to detect a consistent antiviral effect, except in the only SI patient at 160 mug/kg/hr. Because of the lack of antiviral effect and the side effects, the study was stopped.