TNX- 355

Drug Class: **Entry and Fusion Inhibitors**

Drug Description

TNX-355, also known as ibalizumab, is a nonimmunosuppressive, humanized IgG4, anti-CD4, domain 2 monoclonal antibody that prevents HIV entry into human cells. [1] [2] TNX-355 is currently being developed by TaiMed Biologics, through licensing with Genetech, Inc. [3] [4]

HIV/AIDS-Related Uses

TNX-355 is being investigated in Phase II trials as part of combination therapy for the treatment of HIV-1 infection in treatment-experienced patients.[5] [6] TNX-355 was granted fast-track status by the FDA in October 2003.[7] Additional Phase II, dose-finding studies had been initiated by Tanox Inc; however, the drug is now licensed to TaiMed Biologics through Genetic Inc, and no new studies have been initiated yet.[8] [9]

Pharmacology

TNX-355 inhibits HIV entry into lymphocytes and binds to an epitope in domain 2 of the CD4 receptor on a cell's surface, preventing HIV entry into the cell. TNX-355 does not deplete CD4 cells. Unlike anti-CD4 antibodies that target domain 1 of CD4, TNX-355 does not appear to interfere with immunologic functions involving antigen presentation and is not immunosuppressive.[10]

In vitro laboratory studies of HIV-1 subtype B isolates from 82 triple-class-experienced patients evaluated TNX-355 susceptibility based on viral tropism. Of the 82 isolates, 49 were M-tropic, two were T-tropic, and 27 were dual- or mixed-tropic. All isolates were similarly susceptible to TNX-355, and degree of efficacy did not appear associated with tropism.[11]

A Phase Ia study evaluated single 0.3 to 25 mg/kg doses of TNX-355; these doses reduced viral load from baseline by 50% to 90%. This effect was transient, with most levels returning to baseline by Day 28. Significant viral load reductions were observed with the 10 and 25 mg/kg doses and were sustained for 2 to 3 weeks.[12]

In a Phase Ib study, 23% of patients had reduced viral loads by greater than 95%, and 64% had reduced loads by greater than 90%. However, these reductions were also transient, implying that monotherapy may cause quick development of resistance.[13]

An ongoing Phase II, multicenter, randomized, double-blind, placebo-controlled trial is evaluating TNX-355 efficacy and safety in 82 triple-class-experienced patients also on optimized background therapy. The trial is comparing HIV-infected patients who have failed or are failing highly active antiretroviral therapy (HAART) assigned to one of three arms: TNX-355 10 mg/kg once weekly for nine doses followed by 10 mg/kg every other week; TNX-355 15 mg/kg every other week; or placebo. The study is evaluating virologic failure rates and viral load reduction between the two doses and between each dose and placebo. Enrolled patients must have a viral load of 10,000 copies/ml or greater, a CD4 count greater than 50 cells/ml, and triple-class experience with HAART.[14] At the Week 24 interim analysis, viral load decreased by -nearly 10-fold in the 15 mg/kg arm, by 15-fold in the 10 mg/kg arm, and by nearly twofold in the placebo arm. Both treatment arm reductions were statistically greater than the placebo reduction.[15]

Susceptibility of enfuvirtide-resistant viral envelopes to TNX-355 was studied in vitro using G36D, V38A, and N43D substitutions. Envelopes exhibited 11- to 32-fold reduced susceptibility to enfuvirtide but less than twofold reduced susceptibility to TNX-355. No cross resistance to TNX-355 was observed.[16]

Adverse Events/Toxicity

In Phase Ia and Ib safety studies, TNX-355 was well tolerated. No serious adverse effects were reported in the Phase Ia study. Depression recurrence, vasovagal reaction with new onset seizure, and acute renal failure with renal insufficiency were reported in three patients in a Phase Ib, 22-patient study.[17] [18]

TNX- 355

Drug and Food Interactions

In vitro, TNX-355 demonstrates synergy in laboratory and in clinical HIV-1 strains with enfuvirtide, an FDA-approved entry inhibitor.[19] This synergy, along with the differing mechanisms of action and resistance between these two entry inhibitors, supports a strategy of coadministration.[20]

Clinical Trials

For information on clinical trials that involve TNX-355, visit the ClinicalTrials.gov web site at http://www.clinicaltrials.gov. In the Search box, enter: TNX-355 AND HIV Infections.

Dosing Information

Mode of Delivery: Intravenous infusion.[21]

Dosage Form: In clinical trials, TNX-355 has been given intravenously once every other week, sometimes with a loading dose of once-weekly treatment. Doses evaluated include 6, 10, 15, and 25 mg/kg; the 10 and 15 mg/kg doses are being evaluated in an ongoing Phase II study.[22]

Chemistry

CAS Number: 872357-57-8[23]

680188-33-4[24]

Other Names

Hu5A8[25]

TNX 355[26]

Ibalizumab[27]

Further Reading

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Manufacturer Information

TNX-355
Tanox, Inc.
10555 Stella Link
Houston, TX 77025
(866) 312-5200

For More Information

Contact your doctor or an AIDSinfo Health Information Specialist:

• Via Phone: 1-800-448-0440 Monday - Friday, 12:00 p.m. (Noon) - 5:00 p.m. ET

• Via Live Help: http://aidsinfo.nih.gov/live_help Monday - Friday, 12:00 p.m. (Noon) - 4:00 p.m. ET

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