National AIDS Treatment Advocacy Project

1592U89: An update of preliminary safety and antiviral data

1592U89 is a reverse transcriptase inhibitor developed by Glaxo Welcome. Adult study subjects were assigned to one of four dosing regimens of 1592U89 in this trial. Four weeks of monotherapy was followed by randomization to 8 weeks of combination therapy with AZT or AZT-placebo. CD4, viral load and safety data were presented at the Human Retrovirus Conference in January of 1996, for individuals in the first dose regimen of 200 mg tid (3X/day). In Vancouver, Dr. Ramon Torres, a study investigator from St.Vincent's Hospital in New York City, updated study findings. Presented here are data for a few additional study subjects from the 200 mg tid dose regimen, and data for 2 additional dosing regimens: 300 mg bid (2X/day), 400 mg tid. The 4th dosing regimen just recently completed enrollment and data is not yet available.

For a more in-depth discussion of 1592, you can read 1592U89--A New Antiviral For HIV In Development where it says--"Some of the pre-clincal claims by Glaxo Wellcome about this drug are:

1. significant CNS penetration-- crosses blood-brain barrier in rat-
2. 13%, in monkey-- 26%;
3. in vitro synergy with AZT, 3TC, ddI, ddC-- and 2 protease inhibitors tested (141W94, saquinavir);
4. no cross-resistance with AZT; and
5. more than 70% bioavailability.

Glaxo is now planning a pediatric study and further adult studies; because of its CNS penetration, Glaxo is planning a study of the drug's effects in AIDS dementia. Large-scale phase III trials are in the planning stages, and expected to begin in 4th QTR. '96".

The Study

Estimated Median Baseline (preliminary data) CD4 cells/mm3 and HIV RNA (viral load) measured by Roche's RT-PCR assay with a lower limit of 200 copies/ml(undetectable is below 200 copies):

	CD4	HIV RNA (viral load)
200 mg tid group	356 CD4 cells	approximately 125,000 RNA copies/ml

300 mg bid group	381 CD4 cells	31,600 RNA copies/ml
400 mg tid group	355 CD4 cells	31,600 RNA copies/ml

Estimated HIV RNA decreases from baseline(preliminary data): for individuals receiving 1592 monotherapy for 12 weeks

	200 mg tid (n=10)	300 mg bid (n=10)	400 mg bid (n=10)
4 weeks	1.80 log	1.10 log	1.40 log
12 weeks	2.00 log	1.40 log	1.40 log

For individuals who were taking 1592 monotherapy for 4 weeks, and then received combination therapy with AZT for an additional 8 weeks:

	200 mg tid (n=9)	300 mg bid (n=10)	400 mg bid (n=10)
4 weeks	1.70 log	1.60 log	2.20 log
12 weeks	1.90 log	2.30 log	2.70 log

There was about a 100 CD4 increase from baseline regardless of dosing regimen or whether or not subject received 1592 monotherapy or 1592+AZT. The range of median CD4 increases in the 3 cohorts were 79-127.

As you can see a relatively healthy group of individuals were studied in this trial. Individuals with more prior drug experience will be studied in future trials.

Grade 3/4 lab toxicity, n=59:

- 1 person with elevated liver enzymes--Alanine Aminotransferase
- elevation.
- 1 case neutropenia- had grade 2 neutropenia at baseline Adverse event profile:
- nausea, headache, asthenia, rash, dyspepsia, pruritus--most common side effects

4 subjects agreed to have CSF samples collected: CSF approximately concentration was 20% of plasma concentrations, which is about equal to AZT levels in CSF.

Discontinuations

- 4 discontinuations due to adverse events --in the 200 mg tid
- group, 0/10 receiving monotherapy, 2/9 taking the combination: 1 person--parasthesia, fever, rash; 2nd person--nausea.
- 300 mg bid group, no discontinuations
- 400 mg tid group, 0/10 on combination; 2/10 on monotherapy, 1 person on monotherapy discontinued on day 1 due to nausea and fatigue; the other due to rash and fever.