**National AIDS Treatment Advocacy Project**

**1592U89--a new antiviral for HIV in development 4/22/96**

Glaxo Wellcome (GW) is developing a new promising antiviral AIDS drug. It is a nucleoside reverse transcriptase inhibitor called 1592U89. Some of the pre-clinical claims by GW about this drug are:

1. significant CNS penetration-- crosses blood-brain barrier in rat- 13%, in monkey-- 26% (by comparison, AZT crosses the BBB at the rate of 20-25%);
2. in vitro synergy with AZT, 3TC, ddI, ddC-- and 2 protease inhibitors tested (GW's 141W94, Roche's saquinavir);
3. no cross-resistance with AZT; and
4. more than 70% bioavailability.

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

Mike Saag, MD, an AIDS researcher at the University of Alabama-Birmingham, is the lead investigator and has presented the results of an early study (protocol # 02) examining this drug. The trial studied adults with less than 12 weeks prior AZT experience--(only 1 subject had prior AZT-experience of 4 weeks); CD4 200-500; the subjects received 4 weeks 1592U89 monotherapy, to be followed by 8 weeks of 1592 combined with AZT or AZT-placebo, to which individuals are blinded and randomly assigned. Baseline-- CD4 cells 352 (range 219-466), median viral load 5.11 log (RT-PCR), (range 3.58-5.88). 4 different dose regimens are being examined: 200 3X/day--19 subjects, 400 3X/day--n=20, 300 2X/day--n=20, 600 3X/day--so far n=9. This trial was designed primarily to study safety and pharmacokinetics, but CD4 and viral load were also followed.

The 4th dose regimen group, 600 mg. 3X/day, is still recruiting, because all of the available slots have not yet been filled. If you are interested in participating, there is a consideration to bear in mind. There is not yet a provision for individuals to continue receiving 1592, after completing participation in the study; however, GW is in the process of trying to make this provision. For further information about participation, the following is a list of the 7 sites and the investigators at those sites to contact:

- Massachusetts General Hospital in Boston, Dr. Richard D'Aquila; ARCA in Atlanta, Dr. Melanie Thompson; University of Alabama--Birmingham, Dr. Mike Saag; University of Cincinnati, Dr. Judy Feinberg; University of Colorado in Denver, Dr. Chip Schooley; St. Vincent's Medical Center in New York City, Dr. Gabe Torres, VIRX in San Francisco, Dr. Bill Lang.

The data are still accumulating from this study, but below is some early information. Additional data will be presented at the Vancouver AIDS Conference in July, which will include data from the higher doses.
Median CD4 responses (n=19) for the dose regimen of 200 3X/day, at 4 weeks subjects randomized to AZT or AZT-placebo:

- baseline - 352 CD4
- 4 weeks - 435 (increase of 83)
- 8 weeks - 474 (122 increase from baseline)
- 12 weeks - 450 (98 cell increase)

The range of CD4 increases at 4 weeks was from 30 to 160, and at 12 weeks was from 70-160.

As you can observe, this study population is a healthy, less-advanced group.

Median RNA PCR reductions from baseline (5.11 log, n=19):

- 1.3 log at 1 week, n=19
- 1.5 log at 2 weeks, n=15
- 1.75 log at 4 weeks, n=15

After 4 weeks, when subjects were randomized to AZT or AZT-placebo, RNA reductions were:

- 1.8 log at 6 weeks, n=15
- 2.0 log at 8 weeks, n=14
- 2.0 log at 12 weeks, n=7

Study drug discontinuations:

- 1/19 for consent withdrawn
- 1/19 for adverse experience (fever, rash, paresthesia with reoccurrence upon re-challenge).

Grade 3/4 lab toxicity:

- 1/19 for elevated liver enzymes--Alanine Aminotransferase elevation.

Adverse event profile:

- nausea, headache, asthenia, rash, dyspepsia, pruritus--most common

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

1592 and protease inhibitors
1592 does not inhibit the CYP 450 liver enzyme system, so that makes it a more
promising candidate for combination with protease inhibitors. GW may soon conduct an interaction study of 1592 and Crixivan. In preparation for the pre-accelerated approval phase III studies, appropriate studies may be conducted examining the safety of combining 1592 with available protease inhibitors.

As you may know, GW is developing 141W94, which is a protease inhibitor. Although it is in earlier stages of development, it is vital to the interests of people with AIDS or HIV, and particularly individuals with moderate or advanced HIV (who don't have the time to wait for the usual course of research, which is slow) that GW quickly initiate safety and efficacy studies examining the combination of 141W94 with all of the other available protease inhibitors--Invirase, Crixivan, Norvir and Viracept (Agouron). As well, the other protease inhibitor manufacturers also have a responsibility to initiate studies of their inhibitors with others. Abbott has initiated the study of ritonavir/saquinavir, but Merck and Roche have been slower to respond. It is important to our interests to discover, as soon as possible, the potential for these combinations, as well as to uncover any safety concerns. GW and the other drug companies are aware of these concerns and seem sympathetic to them, but the issue requires close follow-up.

**Future trial plans**

GW is starting a new phase II trial of 1592, CNAB 2002, at 5 European sites (60 subjects) in France and Germany. The trial will be a 24 week monotherapy study after which subjects will be permitted to take any other approved medication open-label. It will study a variety of dosing regimens for the purpose of picking a dose for the phase III pivotal trials, which is expected to start in 4th QTR. ’96. GW is now considering the study designs for phase III and whether they will allow for standard of care plus or minus 1592 (which means individuals would be permitted to take any approved antivirals of their choice with 1592 or 1592-placebo).

In July, a key phase II exploratory study will start, subject to FDA approval, which will examine combinations of 1592U89 with AZT, 3TC, ddi, and d4T in individuals, who have at least 6 months experience with these drugs (one year experience with AZT), and with CD4 greater than 100 and viral load greater than 30,000, as measured by RT-PCR; the dose regimen used will be 300 mg. 2X/daily. 40 individuals will be studied for safety and virology. GW wants to discover how individuals, with drug pre-treatment, and who may be resistant to AZT, ddi, 3TC or d4T, may respond to 1592 in combination with these other drugs. Virology studies will be conducted examining resistance profiles and viral load, for the purpose of examining antiviral activity. The trial will last 24 weeks at multiple sites, and probably after 4-weeks of 1592 treatment in combination with other therapy, individuals will be permitted to change their therapy taken along with 1592, but will continue to be followed.

Because of this drug's ability to penetrate the CSF, Glaxo is planning to initiate a trial hopefully this summer, to study clinically diagnosed mild to moderate AIDS dementia in about 90 subjects. After an initial period of 12 weeks, in which subjects will be randomized to 1592 or placebo, all will be offered open-label drug.

A single-dose pharmacokinetics study, with a liquid formulation, has been completed and it has established safety of 1592 for 2 different doses in children 3 months to 13 years. An
ACTG protocol is being planned to study multiple doses in the same age group; about 36 children will be studied at multiple sites. Dr. Mark Klein, of the Texas Children's Hospital, will be the lead investigator. As well, a clinical endpoint study for children is planned for late '96 or early '97. Discussions are underway for a pharmacokinetics study in neonates.

Although the data accumulated to-date is promising, more research is necessary to confirm the efficacy and safety of this drug. Since preliminary in vitro data shows that 1592 is not cross-resistant with AZT, and has very limited cross-resistance with ddi or ddC, a vital question remaining is--will individuals who are resistant to nucleosides and may have depleted its efficacy be able to transition into 1592 with full efficacy? It would be very important for individuals, who have few or no treatment options remaining, to be able to combine 1592 with a protease inhibitor. GW does not expect a production problem for future clinical trials or for post accelerated approval, which I estimate will not occur before June '97; however, our community is concerned about the timeliness of an expanded access program. Future discussions with GW will include this and other subjects, including the development plans for their protease inhibitor--141W94.