FOIA Number: 2007-1550-F

FOIA MARKER

This is not a textual record. This is used as an administrative marker by the William J. Clinton Presidential Library Staff.

Collection/Record Group: Clinton Presidential Records

Subgroup/Office of Origin: National AIDS Policy Office

Series/Staff Member:

Subseries:

OA/ID Number: 19396

FolderID:

Folder Title:
Issues-Economic-Glaxo Wellcome Private Sector [1]

Stack:	Row:	Section:	Shelf:	Position:
S	66	6	5	3

GlaxoWellcome Fax

CORPORATE AFFAIRS

To	Daniel Montoya	**Fax**	202-632-1096
Office of National AIDS Policy			
From	Jennifer McMillan		
Telephone	919-483-2392	**Date**	6/18/97
Fax	919-483-0571	**Total Page**	5

Mission

Glaxo Wellcome is a research-based company whose people are committed to fighting disease by bringing innovative medicines and services to patients throughout the world and to the healthcare providers who serve them.

Values

High Standards
Valuing Customers
Valuing People
Teamwork
Embracing Change
Achievement
Corporate Citizenship

Glaxo Wellcome Inc.

Five Moore Drive
PO Box 13398
Research Triangle Park
North Carolina 27709

Telephone
(919) 483-0608

Fax
(919) 483-0571

Glaxo Wellcome Memo

To: *Daniel Montoya, White House Office of National AIDS Policy*
From: *Jennifer McMillan*
Date: *06/18/97*
Subject: *Follow-up Information*

Daniel,

I have attached some information in response to the issues that we discussed briefly in our telephone conversation earlier this week.

The entry criteria for the open label/compassionate use program is outlined in the "Community Update" and its attachment.

In addition, you asked if we could provide you with some idea about what the company has done in response to community concerns thus far. The second attachment is a consensus letter we received from the community that outlines a program of compassionate use, expanded access and accelerated approval. Overall, we are progressing along this track in our development and access plans for 1592.

Our criteria for compassionate use reflects the community's concerns that patients not be required to fail *all* available therapy before they can access 1592. Instead, we have allowed patients to participate in compassionate use if they still have a drug option to combine with 1592, which reflects the current thinking regarding adding more than one new drug to a regimen.

We built on the community's suggestion by adding a separate compassionate use program for children. And we responded to the community's request to develop a program for patients with AIDS dementia.

We are thoroughly evaluating the development of drug-resistant virus in relation to 1592 use. This is an area of great concern to both the community and Glaxo Wellcome.

Finally, we clearly both agree that moving this product through development to the filing for accelerated approval as quickly as possible is in everyone's best interest.

I hope this information and the attached materials are helpful. Please call me if I can provide more.

Regards,

CC: William Schuyler

GlaxoWellcome

April 28, 1997

Community Update: Glaxo Wellcome 1592 Compassionate Use

We are pleased to provide you with more details about our first steps to broaden access to Glaxo Wellcome's investigational drug, 1592, for the treatment of HIV disease. This letter and attachment outline three Glaxo Wellcome programs. These initiatives will run concurrently with controlled clinical studies, which are now underway for both treatment naive and experienced patients.

As you know, a considerable amount of discussion has taken place involving the company, the HIV community and treaters concerning the best way to provide early access to 1592, while also making best use of limited drug supplies until a larger expanded access program begins in early 1998. The importance of learning more about the appropriate role of 1592 has been raised many times, so we have designed a program for adults that encompasses an open label study which allows for collection of safety and efficacy data. We feel it is important to gather data on a broad population of people in addition to that which is being collected through our clinical trials. These data (viral load and safety) will also provide important information that can be used to help shape the expanded access initiative.

We will be providing access to 1592 initially via three programs: a pediatric program, a program for people with severe AIDS Dementia Complex (ADC) and an adult program. The entry criteria for each program are listed on the attached sheet. The ADC and the pediatric programs will be conducted via a centralized registration procedure, whereby doctors phone to register new participants. The adult program will take place at geographically dispersed centers. We plan to initiate the pediatric program in June. The dementia and the adult programs will begin in July.

The entry criteria for the adult program have been established to allow participants to combine 1592 with other anti-HIV therapies. Specifically, to be eligible to participate individuals must have failed at least two nucleoside reverse transcriptase inhibitors and one protease inhibitor. The adult program will be run through geographically dispersed centers across North America, Europe and Australia. We will provide a list of centers as soon as it is finalized.

To date, there have been approximately 250 people treated with 1592 in the phase II clinical trials. The new initiatives will involve approximately 2,500 people in the three compassionate use/open label studies. This is in addition to the more than 2,000 people in some 20 studies in the ongoing clinical trial program. Through this program, we are attempting to allocate limited supply of drug between the competing needs of extensive clinical trials and this compassionate use/open label program. We view this as the first steps in a broad effort to provide 1592 to the people who need it prior to its approval and until a larger expanded access program can be put in place.

If you have any questions on this program, please contact me or Michael Joyner at 919-483-2987.

Jennifer McMillan
Director, Health Care Coalitions and Advocacy Relations

Glaxo Wellcome Inc.
Five Moore Drive
PO Box 13398
Research Triangle Park
North Carolina 27709

Telephone
919 248 2100

1592
Compassionate Use/Open Label Program
Entry Criteria

Pediatrics

- Viral load > 100,000 copies/ml
- CD4 count < 15%
- Failed at least one NRTI

AIDS Dementia Complex

- Severe dementia (to be defined)
- Diagnosed by a neurologist
- Prior treatment with AZT

ADULTS

- Viral load > 50,000 copies/ml (where measured)
- CD4 count < 100/mm3
- Failed at least two NRTI and one PI

Consensus Statement on 1592 Expanded Access and Accelerated Approval

• Overview

Access to Glaxo Wellcome's 1592U89 ("1592") now in development, potentially represents the only viable option for delaying disease progression for many people living with HIV and AIDS who have exhausted the benefit from currently approved antiviral therapies. In early clinical studies, 1592 has demonstrated a more potent level of antiviral activity than other RT inhibitors, with minimal side effects. It's most important property, however, is that people have not previously been exposed to it and it therefore offers the hope of renewed antiviral activity. This renders the drug critically important to two patient populations: (1) those who have already lost sensitivity to the other drugs of this type, and (2) those who need to use at least one "fresh" or new nucleoside analogue RT inhibitor to make reasonable use of combination therapy with protease inhibitors or non-nucleoside RT inhibitors. Existing evidence clearly suggests that combining such drugs with previously used therapies diminishes their effectiveness and leads to more rapid development of resistance.

The benefit of this drug may be limited due to the development of resistance, a problem common to all currently approved antiviral compounds. While it may take years of additional study to determine its optimal use, this should not delay prompt access to this therapy by people in immediate need. Delaying the availability of this drug until Phase III trials are fully accrued is unacceptable and represents a significant change from past practices. For example, the ddI, d4T, and AZT expanded access programs all took place while trials were still recruiting. We are very concerned that the recent activities of several pharmaceutical companies represents a broad effort to minimize the number of patients served by expanded access programs. Any such effort around 1592 would be a moral affront to the rights and needs of people with HIV/AIDS and their healthcare providers.

We hereby propose the following 1592 expanded access program, to be phased in in stages, with immediate access to those in urgent need.

• First Phase - Compassionate Use/Salvage Therapy

Glaxo Wellcome and the Food and Drug Administration must cooperate and take a more compassionate stance to make this promising compound immediately available in a "salvage program" once a recommended dosing schedule has been established. This compassionate access/salvage program should make drug available as soon as possible for those people who have failed existing therapies and risk near-term danger of death or life-threatening infections.

The development of this drug must take into consideration its unique potential to provide benefit to the acutely compromised segment of the HIV-infected population. Availability of salvage strategies is of the highest priority for people living with HIV. There is no logical or moral reason to withhold this drug from people with advanced illness, people whose lives hang in the balance. Currently, this compound qualifies, by any humane standard, for compassionate use.

This first phase of Compassionate Use/Salvage Therapy should provide 1592 without delay to patients who meet any one of the following two requirements:

1. ***CD4+ Cell Count <50 OR Viral Load >40,000 copies/ml***
   AND Treatment Failure to approved RT Inhibitors AND at least one Protease Inhibitor;
2. ***Diagnosis of AIDS Dementia Complex (ADC), unresponsive to existing therapies.***

We believe evidence of the above conditions can be accomplished with a minimal amount of paperwork. A physician's letter accompanied by one lab report should be sufficient to establish any of the above criteria.

• Second Phase - Expanded Access

This second phase of Expanded Access should provide 1592 during recruitment and conduct of Phase II/III

clinical trials, but no later than ninety (90) days from the start-up of the First Phase, to patients who meet any of the following criteria:

1. ***Patients who do not qualify for or are denied entry in a 1592 clinical trial and have a medical need for 1592, or***
2. ***Patients who do not live within a radius of 15 miles of an active clinical trial site, or***
3. ***Patients whose lives would be immediately jeopardized by randomization to an ineffective treatment regimen, or***
4. ***Patients with a CD4+ Cell count below entry requirements of clinical trials, or***
5. ***Viral Load greater than 20,000 copies/ml., despite use of currently approved therapies, or***
6. ***Treatment Failure or demonstrated genotypic or phenotypic resistance to approved RT inhibitors.***

- **Accelerated Approval**

This compound should be licensed for accelerated approval as soon as possible. FDA approval of this compound should be based on existing regulations governing accelerated approval of new drugs for life-threatening illnesses:

1. ***Clear evidence of benefit on surrogate markers have been demonstrated;***
2. ***Principal toxicities and drug interactions have been defined;***
3. ***Longer-term development plans have been initiated designed to determine the drug's usefulness in promoting clinical and survival improvements and durability of response, as part of a medical strategy for coping with HIV infection.***

****We urge the sponsor to file applications for accelerated approval as soon as possible.***

- **Resistance, Pharmacokinetics and Drug Interactions**

As with all antivirals, the development of drug-resistant strains of virus, drug interactions and pharmocokinetic variances while using this compound may warrant additional considerations. To address this concern, sponsors should also be required, prior to accelerated approval, to present meaningful data on:

1. ***the speed and levels of resistance encountered;***
2. ***the degree of cross-resistance found with other nucleoside analogues;***
3. ***the interaction of the compound with other commonly used anti-HIV medications;***
4. ***bioavailability in men, women, and children and determination of the degree which blood levels vary depending on body weight.***

- **Summation**

Any effort to withhold access to promising compounds is contrary to the interests of HIV-infected people, inconsistent with the Accelerated Approval regulations, and scientifically unwarranted. The long history of the development of the earlier generation of antiviral drugs clearly demonstrates that it is possible to accrue patients and continue conducting clinical trials of compounds, long after their marketing approval. Because of the issues of drug resistance and drug failure over time, new therapies for HIV disease will continue to play a critical role no matter how many drugs become available on the market. New therapies, like 1592, must continue to be made available as rapidly as possible to patients with immediate needs for changed or improved treatment.

AGREED and ACCEPTED this ____ day of _____, 1996:
**** Revised as of 11/27/96***

By: _____ **Of:** _____

Signature **Organization**

Print Name: _____ **Please fax to: 310-471-4565**

GlaxoWellcome Fax

Federal Government Relations and Public Policy

To	Daniel Montoya	**Fax**	(202) 632-1096
From	William J. Schuyler	**Date**	June 25, 1997
Telephone	(202) 783-1277	**Total**	5
Fax	(202) 783-1740	**Pages**	

Daniel:

As promised

William

Mission

Glaxo Wellcome is a research-based company whose people are committed to fighting disease by bringing innovative medicines and services to patients throughout the world and to the healthcare providers who serve them.

Values

High Standards
Valuing Customers
Valuing People
Teamwork
Embracing Change
Achievement
Corporate Citizenship

Glaxo Wellcome Inc.

1500 K St., N.W.
Suite 650
Washington, D.C. 20005

Telephone
(202)783-1277

Fax
(202) 783-1740

Glaxo Wellcome Inc. understands the desire of many within the HIV/AIDS community to gain access to new treatments as soon as possible. We regret that ACT UP New York has chosen to demonstrate as they did today. We have been actively discussing access issues with members of ACT UP, who are aware of the company's plans to address many of the issues that were highlighted today.

Glaxo Wellcome has an obligation to ensure that experimental medicines are safe and effective before they are made available to wide audiences. The adult open label (compassionate use) program for the experimental drug 1592 is beginning in the coming weeks. A larger expanded access initiative will begin early in 1998.

We believe actions such as those that ACT UP took today only serve as a distraction to the people who are working hard to make our new medicines available as quickly as possible for all patients who need them.

ACT UP
AIDS Coalition to Unleash Power

332 Bleecker St. Suite G5
New York, NY 10014
(v/f) 212/966-4871
acupny@panix.com
http://www.acupny.org

For Immediate Release
June 24, 1997

Contact: Activists' cellular phone 917-929-4749
Activists inside Glaxo Wellcome: 212-308-1210/308-5196
Tom Faucett: 212-[redacted] 787-7000 x 1016

AIDS ACTIVISTS TAKE OVER AND HOLD NEW YORK OFFICE OF AIDS PROFITEER GLAXO WELLCOME

ACT UP demands Glaxo Wellcome release new drugs, "1592" and "141 W94"

NEW YORK CITY -- AIDS activists from ACT UP/NY have just seized the offices of Glaxo Wellcome on Park Avenue to protest the pharmaceutical giant's criminally inadequate AIDS drug development and expanded access programs. The take-over by a group of ACT UP members began this morning at 9:15 am. ACT UP demonstrators will not leave the offices until they receive a written commitment from top company officials to immediately launch an expanded access program open to all in need for abacavir (1592) and a new protease inhibitor (141 W94). Glaxo Wellcome's offices are located at 499 Park Avenue (at 59th St), on the 21st floor.

Glaxo will begin an expanded access program in July for the new drug "1592". But the drug will be given to only 2,500 people worldwide. It is widely believed a minimum of 10,000 people in the United States alone need immediate access to this potentially life-saving drug. Activists also are angry at the failure of the company to adequately test the drugs in pregnant and non-pregnant women. Scientists have found differences between men and women in dosing of a significant number of drugs.

Glaxo Wellcome has been aggressive about AIDS drug development since the early days of the epidemic. But activists charge that Glaxo Wellcome has been price-gouging for years. The new drug "1592", already proven stronger than its predecessors AZT and Epivir (3TC), will replace both drugs. According to Bill Behlman of ACT UP/New York, "Glaxo Wellcome's slow development of '1592' is due to the pharmaceutical giant's desire to squeeze the very last profit dollars out of its cash cows AZT and 3TC until their patents run out." Thus far, Glaxo has reaped an astonishing $2.54 billion in sales of AZT. And while sales of AZT and 3TC skyrocketed in 1996, Glaxo slapped a 3% price increase on these overpriced drugs last fall. They now retail for nearly $3,800 and $3,100 per year respectively. Activists also demand the company drastically lower these prices immediately.

-30-

GLAXO BLOCKS DRUG ACCESS
TO PEOPLE WITH AIDS IN DIRE NEED

Glaxo-Wellcome is once again putting greed before people's lives. By announcing that only 2,500 people worldwide will be given access to its new anti-HIV drug, abacavir (1592), before official approval, Glaxo is threatening the lives of thousands of desperate people with AIDS who need this drug NOW! No expanded access program has yet been announced for a drug that is relatively easy to make. Other "expanded access" programs in the past have made drugs available to tens of thousands of people with AIDS who can't wait for FDA approval if they are to stay one step ahead of HIV.

In addition, Glaxo-Wellcome has failed to develop its protease inhibitor 141 W94 which it purchased from Vertex. Even Vertex has been surprised and dismayed about the slow development of their drug. No plans have been announced for expanded access to this powerful protease inhibitor.

Glaxo-Wellcome's slow development of 1592, a drug invented in 1989, is due to the pharmaceutical giant's desire to market AZT, its cash cow, until its patent runs out. So far, AZT has reaped an astonishing $2.6-billion in sales. And though sales of AZT and its newer anti-HIV drug 3TC skyrocketed in 1996, Glaxo has slapped a 3% price increase on these already over-priced drugs now priced at ($3785 and $3054/year)!

Even though women make up 26.5% of new cases of AIDS in urban areas like NYC, no AIDS drug has been tested in enough women to determine safety and efficacy. Effective drug doses in women have sometimes been shown to be different than men, which has meant that the women receiving them have gotten substandard treatment. While the FDA has issued non-binding guidelines to address this problem, Glaxo-Wellcome has failed to test its drugs in pregnant or non-pregnant women in meaningful numbers. While Glaxo-Wellcome is preparing to do dosing trials for 1592 in infants, a pregnant woman who needs the drug for her own health will not be able to access it just like any other PWA will be unable to access it.

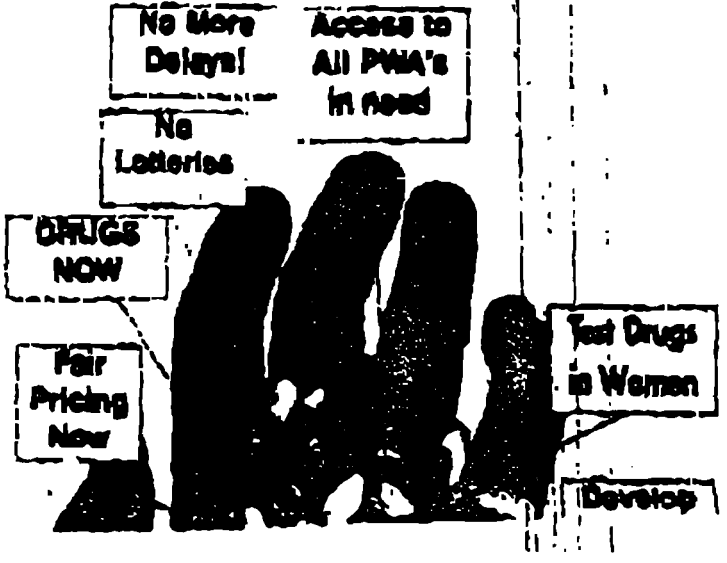
AIDS drugs currently on the market, including many protease inhibitors, are already failing more than ten thousand people with AIDS. For these people, drugs like abacavir and 141 are the only hope. These drugs must be released for expanded access to all who need them now. We demand that Glaxo-Wellcome:

1. Immediately launch an expanded access program for abacavir (1592) open to all in need. Glaxo's current criteria are too strict. A viral load above 30,000 or a tripling of viral load, and CD4 cells below 100, is adequate evidence of treatment failure. Lotteries to determine who gets the drug are not acceptable. Immediately design and implement plans for an expanded access program for 141W94 along the same lines as above.

2. Make future drugs available to people with AIDS who have failed the approved drugs—not after months of community pressure, but rather on a consistent timetable, after safety and preliminary evidence of efficacy have been completed.

3. Test all of its drugs in women in numbers large enough to determine if there are gender specific differences in dosing, toxicity and effectiveness.

4. Test its drugs in combination with drugs from other companies when such combinations are likely to be treatment advances.



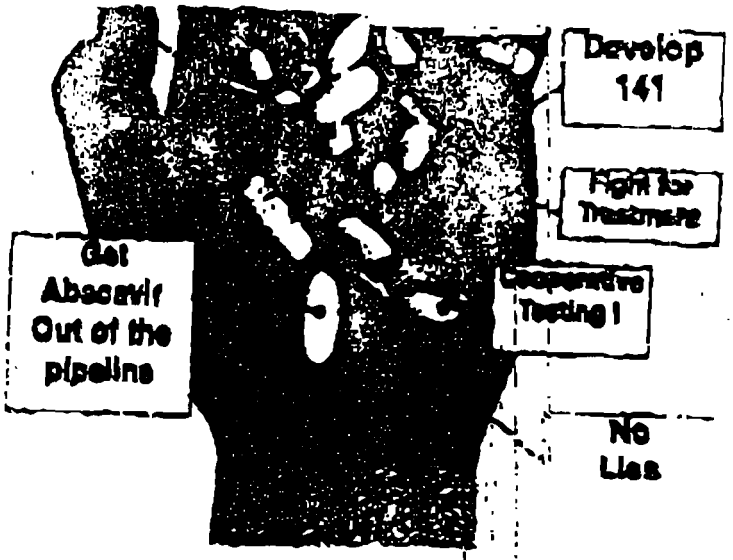
likely to be treatment advances.

5. Lower the prices of AIDS drugs dramatically.

Call Glaxo CEO Robert Ingram at (919) 248-2100 to demand that he immediately act on these demands.

The lives of people with AIDS must not be held hostage for profit.

ACT UP
FIGHT BACK
FIGHT AIDS



For more information, call ACT UP at (212) 966-4873.

GlaxoWellcome Fax

Federal Government Relations and Public Policy

To	Daniel Montoya	**Fax**	(202) 632-1096
From	William J. Schuyler	**Date**	June 25, 1997
Telephone	(202) 783-1277	**Total**	5
Fax	(202) 783-1740	**Pages**	

Daniel:

As promised

William

Mission

Glaxo Wellcome is a research-based company whose people are committed to fighting disease by bringing innovative medicines and services to patients throughout the world and to the healthcare providers who serve them.

Values

High Standards
Valuing Customers
Valuing People
Teamwork
Embracing Change
Achievement
Corporate Citizenship

Glaxo Wellcome Inc.

1500 K St., N.W.
Suite 650
Washington, D.C. 20005

Telephone
(202)783-1277

Fax
(202) 783-1740

Glaxo Wellcome Inc. understands the desire of many within the HIV/AIDS community to gain access to new treatments as soon as possible. We regret that ACT UP New York has chosen to demonstrate as they did today. We have been actively discussing access issues with members of ACT UP, who are aware of the company's plans to address many of the issues that were highlighted today.

Glaxo Wellcome has an obligation to ensure that experimental medicines are safe and effective before they are made available to wide audiences. The adult open label (compassionate use) program for the experimental drug 1592 is beginning in the coming weeks. A larger expanded access initiative will begin early in 1998.

We believe actions such as those that ACT UP took today only serve as a distraction to the people who are working hard to make our new medicines available as quickly as possible for all patients who need them.

ACT UP
AIDS Coalition to Unleash Power

332 Bleecker St. Suite G5
New York, NY 10014

(vm) 212/966-4871
actupny@panix.com
http://www.actupny.org

For Immediate Release
June 24, 1997

Contact: Activists' cellular phone 917-929-4749
Activists inside Glaxo Wellcome: 212-[redacted] 308-5196
Tom Faucett: 212-[redacted] 787-7066 x 1016

AIDS ACTIVISTS TAKE OVER AND HOLD NEW YORK OFFICE OF AIDS PROFITEER GLAXO WELLCOME

ACT UP demands Glaxo Wellcome release new drugs, "1592" and "141 W94"

NEW YORK CITY -- AIDS activists from ACT UP/NY have just seized the offices of Glaxo Wellcome on Park Avenue to protest the pharmaceutical giant's criminally inadequate AIDS drug development and expanded access programs. The take-over by a group of ACT UP members began this morning at 9:15 am. ACT UP demonstrators will not leave the offices until they receive a written commitment from top company officials to immediately launch an expanded access program open to all in need for abacavir (1592) and a new protease inhibitor (141 W94). Glaxo Wellcome's offices are located at 499 Park Avenue (at 59th St.), on the 21st floor.

Glaxo will begin an expanded access program in July for the new drug "1592". But the drug will be given to only 2,500 people worldwide. It is widely believed a minimum of 10,000 people in the United States alone need immediate access to this potentially life-saving drug. Activists also are angry at the failure of the company to adequately test the drugs in pregnant and non-pregnant women. Scientists have found differences between men and women in dosing of a significant number of drugs.

Glaxo Wellcome has been aggressive about AIDS drug development since the early days of the epidemic. But activists charge that Glaxo Wellcome has been price-gouging for years. The new drug "1592", already proven stronger than its predecessors AZT and Epivir (3TC), will replace both drugs. According to Bill Bahlman of ACT UP/New York, "Glaxo Wellcome's slow development of '1592' is due to the pharmaceutical giant's desire to squeeze the very last profit dollars out of its cash cows AZT and 3TC until their patents run out." Thus far, Glaxo has reaped an astonishing $2.54 billion in sales of AZT. And while sales of AZT and 3TC skyrocketed in 1996, Glaxo slapped a 3% price increase on these overpriced drugs last fall. They now retail for nearly $3,800 and $3,100 per year respectively. Activists also demand the company drastically lower these prices immediately.

-30-

GLAXO BLOCKS DRUG ACCESS
TO PEOPLE WITH AIDS IN DIRE NEED

Glaxo-Wellcome is once again putting greed before people's lives. By announcing that only 2,500 people worldwide will be given access to its new anti-HIV drug, abacavir (1592), before official approval, Glaxo is threatening the lives of thousands of desperate people with AIDS who need this drug NOW. No expanded access program has yet been announced for a drug that is relatively easy to make. Other "expanded access" programs in the past have made drugs available to tens of thousands of people with AIDS who can't wait for FDA approval if they are to stay one step ahead of HIV.

In addition, Glaxo-Wellcome has failed to develop its protease inhibitor 141 W94 which it purchased from Vertex. Even Vertex has been surprised and dismayed about the slow development of their drug. No plans have been announced for expanded access to this powerful protease inhibitor.

Glaxo-Wellcome's slow development of 1592, a drug invented in 1989, is due to the pharmaceutical giant's desire to market AZT, its cash cow, until its patent runs out. So far, AZT has reaped an astonishing $2.6-billion in sales. And though sales of AZT and its newer anti-HIV drug 3TC skyrocketed in 1996, Glaxo has slapped a 3% price increase on these already over-priced drugs now priced at ($3785 and $3054/year)!

Even though women make up 26.5% of new cases of AIDS in urban areas like NYC, no AIDS drug has been tested in enough women to determine safety and efficacy. Effective drug doses in women have sometimes been shown to be different than men, which has meant that the women receiving them have gotten substandard treatment. While the FDA has issued non-binding guidelines to address this problem, Glaxo-Wellcome has failed to test its drugs in pregnant or non-pregnant women in meaningful numbers. While Glaxo-Wellcome is preparing to do dosing trials for 1592 in infants, a pregnant woman who needs the drug for her own health will not be able to access it just like any other PWA will be unable to access it.

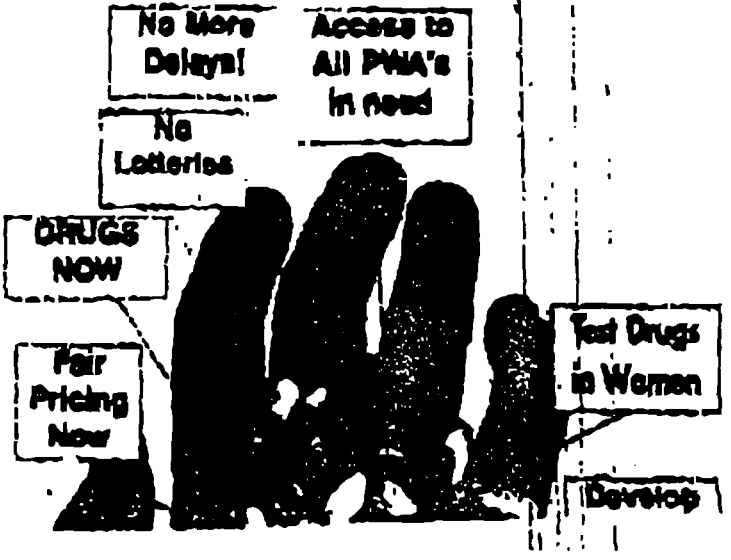
AIDS drugs currently on the market, including many protease inhibitors, are already failing more than ten thousand people with AIDS. For these people, drugs like abacavir and 141 are the only hope. These drugs must be released for expanded access to all who need them now. We demand that Glaxo-Wellcome:

1. Immediately launch an expanded access program for abacavir (1592) open to all in need. Glaxo's current criteria are too strict. A viral load above 30,000 or a tripling of viral load, and CD4 cells below 100, is adequate evidence of treatment failure. Lotteries to determine who gets the drug are not acceptable. Immediately design and implement plans for an expanded access program for 141W94 along the same lines as above.

2. Make future drugs available to people with AIDS who have failed the approved drugs—not after months of community pressure, but rather on a consistent timetable, after safety and preliminary evidence of efficacy have been completed.

3. Test all of its drugs in women in numbers large enough to determine if there are gender specific differences in dosing, toxicity and effectiveness.

4. Test its drugs in combination with drugs from other companies when such combinations are likely to be treatment advances.



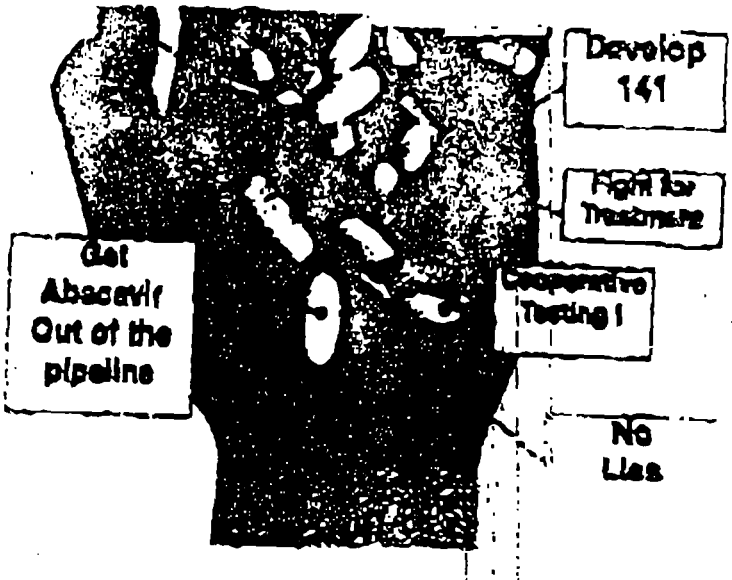
likely to be treatment advances.

5. Lower the prices of AIDS drugs dramatically.

Call Glaxo CEO Robert Ingram at (919) 248-2100 to demand that he immediately act on these demands.

The lives of people with AIDS must not be held hostage for profit.

ACT UP
FIGHT BACK
FIGHT AIDS



For more information, call ACT UP at (212) 966-4873.

ATTENTION MICHAEL DIZ -

Michael -

Thanks for your help. Here's a note with questions to on-pass to Sandy. Take care.

Sandy -

Hi. First, just FYI, I'm hearing good things from activists here about your advocacy around 1592. There's a real fever pitch about the importance of the drug. Good luck with Glaxo.

Now it's my turn, briefly. I'm doing a piece for POZ on women in clinical trials - a follow up to the Women & HIV Conference. A couple of questions, please.

1. I talked to Scott Hitt out here and he says he thinks women are now included in government-sponsored clinical trials - by about 12% . He also said that the inclusion of women should be reflective of the women/HIV population - and if they're not included - it should be mandated that they should be. SO: considering that the death rate for women is up by 3% and considering that women die faster after diagnosis, is a 12% inclusion rate sufficient?

2. If the FDA's mission is to regulate drug approval - with the safety of the drug a primary concern - how can the FDA approve drugs which have been basically only tested and analyzed in half the population, i.e. men? Also - government health officials seem concerned about including, as the activists put it, "potentially pregnant" women - while the fact that HIV-infected men are also sperm providers is not considered. What can be done to make the FDA live up to it's mission, especially concerning trials for dosage levels and frequency with which drugs should be taken by women?

3. Can the above be considered unethical, especially in light of the President's pledge about biomedical ethics after the Tuskegee apology?

4 There have been several protests, meetings, and recommendations - including those proposed by the National Drug Development Task Force in 1994 to change the FDA regulations to require trial sponsors to include women and to change labeling to provide information pertinent to women (example: labels on Monistat 7 specifically note that a recurring yeast infection may be a sign of diabetes or HIV - BUT less expensive over the counter remedies do note include such info - and, as you know, poor women will thus self-medicate and present at emergency rooms with full -blown AIDS). In Sept. 1995 FDA issued amendments regarding drug application and approval regulations - with public comment due by Dec. 1995. However - no new amendments have yet been issued. Can you do anything to push this along?

5. Regarding 1592 and 141 W94 - is Glaxo testing the drugs adequately in women- ie in significant numbers for gender-specific analysis in pregnant and non-pregnant women? As you know, there are a number of women (the blond Donna I introduced you to at the Women & HIV Conference, for example) who have been having a terrible time tolerating existing drugs and have developed drug resistance. They are very anxious about 1592. And, again as I know you know, the horror of drug failure or intolerance is compounded by the fact that the women are not as organized as the men and don't have the same support - so like men in the beginning of the crisis, they are suffering in silence, shame, and too often, ignorance while still going to work and caring for the kids. Clinical trials are often their only access to a healthcare package (physical, dental, etc). Will Glaxo expand the compassionate use access to include poor women?

These are not easy questions, I know. But I would very much appreciate a response ASAP. Meanwhile - take care and thanks for taking on such a big job.

Regards,

Karen Ocamb

Karen Ocamb
(213) 656-2692
FAX: (213) 656-9056
e-mail: LNKOcamb@aol.com

You had wanted to speak w/
Glaxo-Wellcome: 1592
(William Schuyler)
Before the Conference Call
@ 3:00pm...
He will be available
for the next ½ hr or so
@ 785-1277

Senior Research
$ VP Antiviral Research
$ Director Research
Dave Ficel - FDA or acting
administrat

Memorandum

TO: Sandra L. Thurman and Daniel C. Montoya

FROM: Michael Diz

DATE: June 25, 1997

RE: Conference call with Jeff Getty and other activists- June 25, 1997

COMMENTS:

*Glaxo has reportedly verbally agreed with a Canadian activist to set up a triage drug assistance program and to pay for those in the compassionate use program to travel to the drug distribution sites.

*In the Expanded Access Program, which will begin in the first quarter of 1998, the drugs will be available through local physicians.

*No such agreements are known to have been reached with US activists.

*Those on the call requested that the ONAP set up a meeting this week between Glaxo and the community.

*Those on the call also requested that the ONAP insist that Glaxo produce a written response to the "demand letter" which was sent to them several days ago.

1592 ACCESS COALITION

To: Sandy Thurmond	From : Linda Grinberg	
Company: White House-AIDS Office	Telephone: 310-471-6565	
F x Number: 1-202-632-1098	Fax Number: 310-471-4565	
Subject : Conf. Call	Date: 6/18/97	Pages: 1 2

Please see attached list of participants in today's conference call scheduled at 6:00 EST/3:00 PST.

Reminder: The phone number to call in to is (800) 360-0565. Please ask for the 1592 Access Coalition call with Jeff Getty & Linda Grinberg, moderators.

If there is any problem in accessing the call, please call (800) 825-2125 and tell operator the conf. call # is 811-8888.

We look forward to speaking with you later today.

See Richard Sykes
Clare - 011-44-171-493-4060
011-44-171-408 0228 FAX

- triage
- travel (compassionate)
- expanded access

Just 6 protocols
to
sites

I 592 ACCESS COALITION

Name	Affiliation	Phone	Fax
1. Meg Atkinson	AIDS Action Now!/Toronto	416-487-8065	416-533-2127
2. Ron Baker	S.F. AIDS Foundation	415-487-8065	415-487-8069
3. Bill Bahlman	Treatment & Data Committee	212-929-4952	212-929-4952
4. Peter Cashman	ACT UP Los Angeles	213-669-7301	213-669-7302
5. Sally Cooper	PWA Health Group	212-255-0520	212-255-2080
6. Leigh Paidolfino-Danas	U.K.	44-171-793-7444	
7. Paul Davis	ACT UP Philadelphia	215-731-1844	215-731-1845
8. Martin Delaney	Project Inform	415-331-0184	415-331-2114
9. Jeff Getty	ACT UP Golden Gate	510-653-6278	510-653-6099
10. David Gilden	Gay Men's Health Crisis	718-624-6578-h 212-367-1452-o	918-624-8399
11. Linda Grinberg	Project Inform/F.A.I.R.	310-471-6565	310-471-4565
12. John Iverson	ACT UP East Bay	510-568-1680	
13. Cleve Jones	Names Project	707-865-9047	707-865--0541
14. Kate Krauss	ACT UP Philadelphia	215-731-1844	215-731-1845
15. James Learned	PWA Health Group	212-255-0520	212-255-2080
16. Jules Levin	N.A.T.A.P.	718-624-8541	718-624-8399
17. Andy Lipschitz, MD		516-935-6359	516-938-5470
18. L. Joel Martinez	Center for AIDS	713-527-8219	713-521-3679
19. Eileen Mitzman	Mother's Voices	212-737-3335	212-737-1092
20. Lili Rundback	Mother's Voices	212-730-2777	212-730-4378
21. Matthew Sharp	ACT UP Golden Gate	415-626-4053	415-626-0451
22. Theo Smart	Treatment Action Group	212-260-2607	212-673-8921

Fax Transmittal Cover Sheet

To: Sandy Thurman , - Office of AIDS Policy
From: Kate Krauss
Facsimile Number: 215-731-1845
Date: Fri, Jun 20, 1997 • 12:19 PM
Number of pages, including cover: 2
If there is difficulty with this transmission, please call: 215-731-1844

GLAXO WELLCOME'S REFUSAL TO RELEASE ITS NEW DRUG HAS PEOPLE WITH AIDS LAYING IN THE AISLES.

GLAXO: RELEASE 1592!

Glaxo Wellcome is the manufacturer of AZT, 3TC, and other drugs that with people with HIV take. Glaxo is also one of the largest and most profitable companies of any kind in the world. Glaxo has a new experimental drug, which right now is called "1592". The drug is very powerful at reducing the amount of HIV in a person's body.

1592 is a very important drug to people with HIV, especially those who have been HIV + for a while. Many PWAs have already developed resistance to AZT, DDI, and other similar drugs, called "reverse transcriptase inhibitors" or RTIs. 1592 is a new and more powerful drug in the same class as the older RTIs. People who no longer benefit from AZT or 3TC will probably be helped by taking 1592.

We know that the new protease inhibitors only work well when used in combination with other anti-HIV drugs from different classes. People who are resistant to the older RTIs have nothing to combine the new protease inhibitors or NNRTIs with. Without enough treatment options, people with HIV develop resistant virus and get sick.

AIDS activists from across the country have spent the last year asking Glaxo to release 1592 to sick people with HIV who don't have very many options left. These is called an "Expanded Access Program," and it allows desparate people to get new drugs before they are approved by the FDA.

Drug companies don't like expanded access programs because they usually have to give the drug away for free. In the past, drug companies were forced by activists to create large expanded access programs that helped tens of thousands of people.

At first, Glaxo said they would only make available enough drug to supply 2500 people world wide! After being shut out of a trade show by demonstrators, the company shifted its figures and then claimed that 10,000 would be able to get 1592, but the drug would be rationed: 200 slots per week. When Canadian activists threatened to demonstrate the company found yet <u>another</u> way to count. Now there is enough drug for 20,000 people, but only if people with AIDS wait until <u>next year</u> to start the program!

Thousands more need this drug! Call Glaxo Wellcome today and tell them that they must provide 1592 for any person with AIDS who needs it, NOW!

Call Robert Ingram, Glaxo President & CEO, (919) 248-2100 or fax (919) 549-7459

ACT UP Philadelphia is the AIDS Coalition to Unleash Power. ACT UP is an all volunteer group of individuals united in anger and committed to direct action to end the AIDS crisis. We take no money from government or pharmaceutical sources. *Get involved!* We meet every Monday at 7pm at St Luke's Church on 13th street between Pine and Spruce. Refreshments provided. Tokens available on request.

GlaxoWellcome Fax

Federal Government Relations and Public Policy

To	Daniel Montoya	Fax	(202) 632-1096
From	William J. Schuyler	Date	June 24, 1997
Telephone	(202) 783-1277	Total Pages	4
Fax	(202) 783-1740		

Daniel:

I promised to get you some updated information about industry's commitment to assuring access to HIV treatments. I've enclosed a couple of new documents describing what Glaxo Wellcome is doing on its own to help people with HIV and AIDS, and describing some federal programs we participate in that help assure access to medications. I hope these help.

William

Mission

Glaxo Wellcome is a research-based company whose people are committed to fighting disease by bringing innovative medicines and services to patients throughout the world and to the healthcare providers who serve them.

Values

High Standards
Valuing Customers
Valuing People
Teamwork
Embracing Change
Achievement
Corporate Citizenship

Glaxo Wellcome Inc.

1500 K St., N.W.
Suite 650
Washington, D.C. 20005

Telephone
(202)783-1277

Fax
(202) 783-1740

GlaxoWellcome

GLAXO WELLCOME HIV MEDICATION ACCESS EFFORTS

Rapidly emerging data concerning the beneficial effects of multi-drug combinations in the management of HIV disease have increasingly focused attention on the health care resources needed to ensure that people living with HIV disease receive state-of-the-art medical care. As the leader in the discovery and development of medications for the management of HIV disease, Glaxo Wellcome has worked with government, academia and the HIV community for many years to enhance knowledge and education about the effective use of HIV medications. In addition to its significant ongoing research and development programs, Glaxo Wellcome has undertaken a number of initiatives to work with those involved in the delivery of care to address the issue of medication access and reimbursement for people living with HIV disease.

National

Since 1987, the company has contributed more than $13 million to grass roots, state and national AIDS community programs. Access to care initiatives are a key focus of contributions efforts.

More than 30,000 individuals with HIV disease in the United States received Epivir® (lamivudine, 3TC) at no cost through an open label compassionate use program in place from October 1993 through December 1995. The Glaxo Wellcome program was the largest expanded access program ever conducted for an HIV therapy. Plans are currently underway for open label and expanded access programs in children and adults for 1592, a compound in development for the treatment of HIV infection.

Substantial medication discounts have been provided to health care facilities, including those serving individuals with HIV disease, which are under Federal Contract.

The company is an active participant in the Inter-Company Collaboration for AIDS Drug Development, a group of pharmaceutical companies formed in 1993 to facilitate early combination and comparative studies of antiviral agents for the treatment of HIV disease. This group, although not focused on funding, shares preclinical and clinical data, drug supplies and assays to facilitate the study of combination therapies.

The company is also an active participant in the Forum for Collaborative HIV Research, a partnership of public and private organizations including research-based pharmaceutical companies, government agencies and patient advocates to oversee clinical research into therapeutic strategies to treat and manage HIV infection and AIDS. The forum was formed in early 1997 when Vice President Al Gore met with pharmaceutical executives and government officials to discuss drug development efforts.

Glaxo Wellcome is actively involved in the AIDS Drug Assistance Program Future Funding Working Group, a coalition of industry and community representatives working to increase Ryan White funds. Activities have included visits with key Administration and Congressional leaders as well as ongoing efforts to quantify the need for increased funding and the economic benefits of HIV therapy.

Glaxo Wellcome Inc.

1500 K Street NW
Suite 650
Washington DC 20005

Telephone
202 783 1777

Fax
202 783 1740

State

Glaxo Wellcome provided rebates to Medicaid and state entitlement programs of more than $20 million on its HIV medications during the 12-month period of April 1996 through March 1997.

The company has voluntarily extended rebates in excess of $6 million to 20 states that did not have distribution mechanisms in place to take advantage of Federal rebate programs.

Glaxo Wellcome state field managers are actively working with states that are experiencing fiscal difficulties on an individual basis to identify and assess various legislative and programmatic initiatives to help them meet their patients' health care needs.

Glaxo Wellcome has funded numerous initiatives at the state and local level to improve access to medications and quality of health care for people with HIV disease. Examples include a training program for case managers in California, a New Jersey program that provides support to women parolees, and many contributions to improve case management and medical services at AIDS service agencies and community-based organizations throughout the country. These contributions often provide a needed boost to programs faced with a decline in government funding and increasing demands for services.

Glaxo Wellcome has developed the Ryan White Title II AIDS Drug Assistance Budget Model, a pharmacoeconomic model that assists in determining costs and demonstrates benefits including patient outcomes of HIV therapies. At the request of state ADAP directors, we work in conjunction with these programs to estimate the budget and funding necessary to support a given formulary or to compare the health and economic outcomes associated with multiple, alternative formularies.

Patient Assistance

Glaxo Wellcome has its own Patient Assistance Program to make its prescription medications, including all HIV medications, available to patients who do not have or qualify for private insurance or government-funded programs. Last year, the company made available products valued at more than $18 million through this program to qualified participants.

The company is dedicated to providing patients with information and guidance in finding alternative reimbursement sources for needed medicines. The Patient Assistance Program has an active case management program and the ability to work with individuals on a case-by-case basis. Last year we actively assisted more than 550 HIV patients through our reimbursement case management services.

Although the company recognizes that many states are experiencing fiscal difficulties, the Patient Assistance Program is not intended to supplement or replace government-sponsored programs. Rather, it is a philanthropic activity to help individuals who simply are not eligible for any other program.

FEDERALLY MANDATED DISCOUNTS FOR HIV AND AIDS TREATMENTS

Public Health Service Drug Pricing Program

Under the PHS Drug Pricing Program, a large number of health care providers that provide care to people with HIV or AIDS are eligible to receive mandatory discounts from pharmaceutical companies. These discounts are available to health care providers identified as eligible by the Public Health Service. These providers are given discounts comparable to those available to state Medicaid programs. equal to the lowest price available in the private marketplace less any inflation (CPI) reduction.

Many public hospitals participate in a number of these PHS programs and, thus, have access to these discounts. Entities meeting the requirements of the following programs may receive PHS discounted drug prices.

- *Federally Qualified Health Center Program*: these programs include Migrant Health Centers, Community Health Centers, Health Services for the Homeless. and Health Services for Residents of Public Housing.

- *Health Care Services Program*: AIDS medications are available under Titles I, II, and III of the Ryan White CARE Act which provides funds to state AIDS Drug Assistance Programs (ADAP).

- *Comprehensive Hemophilia Diagnostic Treatment Centers.*

- *Projects and Programs for the Prevention and Control of Sexually Transmitted Diseases.*

- *Family Planning Programs.*

- *Native American Health Care Clinics.*

- *Tuberculosis Clinics.*

- *Disproportionate share hospitals:* these hospitals serve a larger than average number of poor or uninsured people.

Medicaid

OBRA '90 requires pharmaceutical manufacturers to pay rebates to state Medicaid programs for all drugs they purchase. These Medicaid discounts are either the larger of 15.1 percent of the average wholesale price of a drug or the highest discount given to any private purchaser of a drug. Both these discounts are further reduced by any price increases greater than inflation.

GlaxoWellcome Fax

Federal Government Relations and Public Policy

To	Daniel Montoya	**Fax**	(202) 632-1096
From	William J. Schuyler	**Date**	June 25, 1997
Telephone	(202) 783-1277	**Total**	5
Fax	(202) 783-1740	**Pages**	

Daniel:

As promised

William

Mission

Glaxo Wellcome is a research-based company whose people are committed to fighting disease by bringing innovative medicines and services to patients throughout the world and to the healthcare providers who serve them.

Values

High Standards
Valuing Customers
Valuing People
Teamwork
Embracing Change
Achievement
Corporate Citizenship

Glaxo Wellcome Inc.

1500 K St., N.W.
Suite 650
Washington, D.C. 20005

Telephone
(202)783-1277

Fax
(202) 783-1740

Glaxo Wellcome Inc. understands the desire of many within the HIV/AIDS community to gain access to new treatments as soon as possible. We regret that ACT UP New York has chosen to demonstrate as they did today. We have been actively discussing access issues with members of ACT UP, who are aware of the company's plans to address many of the issues that were highlighted today.

Glaxo Wellcome has an obligation to ensure that experimental medicines are safe and effective before they are made available to wide audiences. The adult open label (compassionate use) program for the experimental drug 1592 is beginning in the coming weeks. A larger expanded access initiative will begin early in 1998.

We believe actions such as those that ACT UP took today only serve as a distraction to the people who are working hard to make our new medicines available as quickly as possible for all patients who need them.

ACT UP
AIDS Coalition to Unleash Power

332 Bleecker St. Suite G5
New York, NY 10014

(v/f) 212/966-4871
actupny@panix.com
http://www.actupny.org

For Immediate Release
June 24, 1997

Contact: Activists' cellular phone 917-929-4749
Activists inside Glaxo Wellcome: 212-[redacted]
Tom Faucett: 212-[redacted] 787-7000 x 1016

AIDS ACTIVISTS TAKE OVER AND HOLD NEW YORK OFFICE OF AIDS PROFITEER GLAXO WELLCOME

ACT UP demands Glaxo Wellcome release new drugs, "1592" and "141 W94"

NEW YORK CITY -- AIDS activists from ACT UP/NY have just seized the offices of Glaxo Wellcome on Park Avenue to protest the pharmaceutical giant's criminally inadequate AIDS drug development and expanded access programs. The take-over by a group of ACT UP members began this morning at 9:15 am. ACT UP demonstrators will not leave the offices until they receive a written commitment from top company officials to immediately launch an expanded access program open to all in need for abacavir (1592) and a new protease inhibitor (141 W94). Glaxo Wellcome's offices are located at 499 Park Avenue (at 59th St.), on the 21st floor.

Glaxo will begin an expanded access program in July for the new drug "1592". But the drug will be given to only 2,500 people worldwide. It is widely believed a minimum of 15,000 people in the United States alone need immediate access to this potentially life-saving drug. Activists also are angry at the failure of the company to adequately test the drugs in pregnant and non-pregnant women. Scientists have found differences between men and women in dosing of a significant number of drugs.

Glaxo Wellcome has been aggressive about AIDS drug development since the early days of the epidemic. But activists charge that Glaxo Wellcome has been price-gouging for years. The new drug "1592", already proven stronger than its predecessors AZT and Epivir (3TC), will replace both drugs. According to Bill Behlman of ACT UP/New York, "Glaxo Wellcome's slow development of '1592' is due to the pharmaceutical giant's desire to squeeze the very last profit dollars out of its cash cows AZT and 3TC until their patents run out." Thus far, Glaxo has reaped an astonishing $2.54 billion in sales of AZT. And while sales of AZT and 3TC skyrocketed in 1996, Glaxo slapped a 3% price increase on these overpriced drugs last fall. They now retail for nearly $3,800 and $3,100 per year respectively. Activists also demand the company drastically lower these prices immediately.

-30-

GLAXO BLOCKS DRUG ACCESS
TO PEOPLE WITH AIDS IN DIRE NEED

Glaxo-Wellcome is once again putting greed before people's lives. By announcing that only 2,500 people worldwide will be given access to its new anti-HIV drug, abacavir (1592), before official approval, Glaxo is threatening the lives of thousands of desperate people with AIDS who need this drug NOW! No expanded access program has yet been announced for a drug that is relatively easy to make. Other "expanded access" programs in the past have made drugs available to tens of thousands of people with AIDS who can't wait for FDA approval if they are to stay one step ahead of HIV.

In addition, Glaxo-Wellcome has failed to develop its protease inhibitor 141 W94 which it purchased from Vertex. Even Vertex has been surprised and dismayed about the slow development of their drug. No plans have been announced for expanded access to this powerful protease inhibitor.

Glaxo-Wellcome's slow development of 1592, a drug invented in 1989, is due to the pharmaceutical giant's desire to market AZT, its cash cow, until its patent runs out. So far, AZT has reaped an astonishing $2.6-billion in sales. And though sales of AZT and its newer anti-HIV drug 3TC skyrocketed in 1996, Glaxo has slapped a 3% price increase on these already over-priced drugs now priced at ($3785 and $3054/year)!

Even though women make up 26.5% of new cases of AIDS in urban areas like NYC, no AIDS drug has been tested in enough women to determine safety and efficacy. Effective drug doses in women have sometimes been shown to be different than men, which has meant that the women receiving them have gotten substandard treatment. While the FDA has issued non-binding guidelines to address this problem, Glaxo-Wellcome has failed to test its drugs in pregnant or non-pregnant women in meaningful numbers. While Glaxo-Wellcome is preparing to do dosing trials for 1592 in infants, a pregnant woman who needs the drug for her own health will not be able to access it just like any other PWA will be unable to access it.

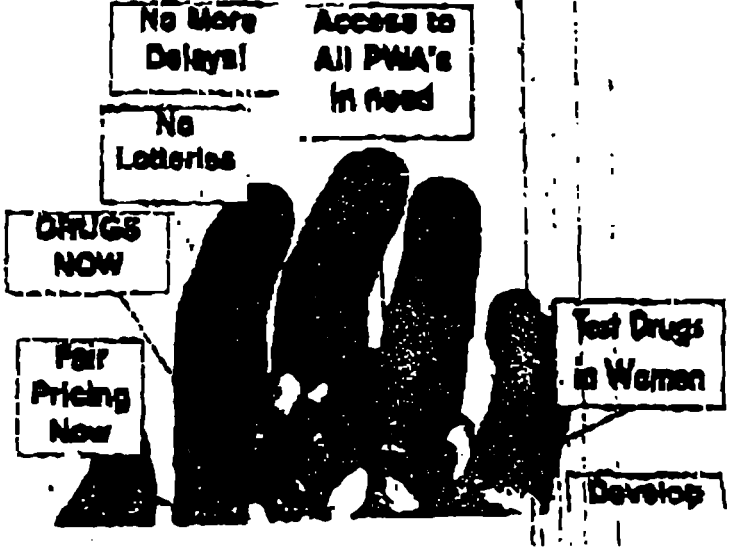
AIDS drugs currently on the market, including many protease inhibitors, are already failing more than ten thousand people with AIDS. For these people, drugs like abacavir and 141 are the only hope. These drugs must be released for expanded access to all who need them now. We demand that Glaxo-Wellcome:

1. Immediately launch an expanded access program for abacavir (1592) open to all in need. Glaxo's current criteria are too strict. A viral load above 30,000 or a tripling of viral load, and CD4 cells below 100, is adequate evidence of treatment failure. Lotteries to determine who gets the drug are not acceptable. Immediately design and implement plans for an expanded access program for 141W94 along the same lines as above.

2. Make future drugs available to people with AIDS who have failed the approved drugs—not after months of community pressure, but rather a consistent timetable, after safety and preliminary evidence of efficacy have been completed.

3. Test all of its drugs in women in numbers large enough to determine if there are gender specific differences in dosing, toxicity and effectiveness.

4. Test its drugs in combination with drugs from other companies when such combinations are likely to be treatment advances.



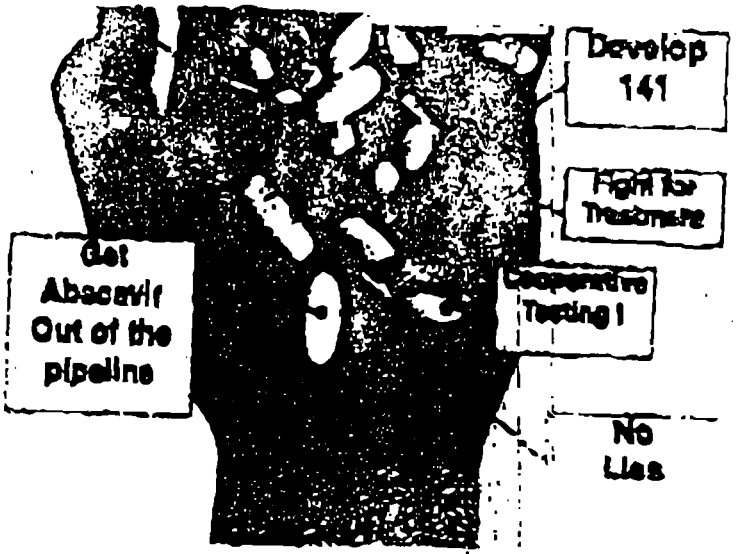
likely to be treatment advances.

5. Lower the prices of AIDS drugs dramatically.

Call Glaxo CEO Robert Ingram at (919) 248-2100 to demand that he immediately act on these demands.

The lives of people with AIDS must not be held hostage for profit.

ACT UP
FIGHT BACK
FIGHT AIDS



For more information, call ACT UP at (212) 966-4873.

GlaxoWellcome Fax

Federal Government Relations and Public Policy

To	Daniel Montoya	**Fax**	(202) 632-1096
From	William J. Schuyler	**Date**	June 9, 1997
Telephone	(202) 783-1277	**Total**	2
Fax	(202) 783-1740	**Pages**	

Daniel:

Here is the list of attendees for tomorrow's meeting with Sandy Thurman. Please call if you need anything else.

William

Mission

Glaxo Wellcome is a research-based company whose people are committed to fighting disease by bringing innovative medicines and services to patients throughout the world and to the healthcare providers who serve them.

Values

High Standards
Valuing Customers
Valuing People
Teamwork
Embracing Change
Achievement
Corporate Citizenship

Glaxo Wellcome Inc.

1500 K St., N.W.
Suite 650
Washington, D.C. 20005

Telephone
(202)783-1277

Fax
(202) 783-1740

NAME	TITLE
Marc Rubin, M.D.	Vice President, U.S. Clinical Research
Stephen W. Lafon	Senior Clinical Program Head
David M. Cocchetto, Ph.D.	Director, Regulatory Affairs
Jennifer L. McMillan	Director, Health Care Coalition
William J. Schuyler	Director, Federal Government Relations

Fax from Linda Grinberg

To: Sandy Thurmond	From : Linda Grinberg	
Company: The White House, AIDS Czar	Telephone: 310-471-6565	
Fax Number: 1-202-632-1096	Fax Number: 310-471-4565	
Subject : Glaxo Wellcome - 1592	Date: 5/22/97	Pages: 1

Sandy:

Per our conversation last Friday, I thought this article which appeared in the S.F. Bay Times, as well as Bay Windows Boston, might be of interest. Anything to report yet?

Thanking you in advance for your guidance and leadership on this critical issue...

Best regards,

Linda

- FDA -
IND 3 yrs —
Classical Dev for AIDS drugs -
Phase III Clinical drug -
Application for excelerated approval in about a year
16-24 week data on patients —
VW02 - in 86 was an exception —
'91 Parallel drug statement
3TC BW 30,000
* Bridge end of phase III to approval —

The Fight for 1592

AIDS Activists Battle Glaxo over Access To Anxiously Awaited New Drug

PHOTO BY MARC GELLER

Cleve Jones

PHOTO BY RDNK

Matthew Sharp

BY BRUCE MIRKEN

A decade after the high price of AZT caused AIDS activists to declare war on Burroughs Wellcome, the AIDS community is again gearing up for battle with the pharmaceutical giant—now known as Glaxo Wellcome—over access to what San Francisco AIDS Foundation director of treatment education and advocacy Ron Baker has called "the most important AIDS drug in the research pipeline."

That drug, known by the code name 1592U89 and commonly referred to simply as 1592, belongs to the class of drugs called nucleoside analogs, the same category as AZT, 3TC, ddC, ddI and d4T. In an article published last December Baker called it "the only nucleoside analog in the research pipeline that appears safe and potent." In early tests 1592 has demonstrated far more anti-HIV punch than any of the earlier "nukes," and appears to be less toxic as well. In one study of 1592 combined with AZT, the two-drug combination reduced HIV blood levels by as much as 99 percent in 29 volunteers, far better than any 2-nuke combination ever tested.

The company has responded to pleas for access to the drug with a tiny program that San Francisco AIDS specialist Dr. Virginia Cafaro dismisses as "pathetic," but which Glaxo insists is all it can do for now.

DESPERATE PATIENTS

While another nuke may seem like small potatoes in the age of protease inhibitors, the protease drugs, along with the recently approved non-nucleoside reverse transcriptase inhibitors nevirapine and delavirdine, must be combined with other drugs to get their full effect. The nukes are a key ingredient of these combination regimens; but plenty of people with AIDS have used up all of the older nukes, the HIV in their bodies gradually having become resistant to each of the drugs. For them 1592 represents the only hope for building a drug cocktail that can keep them alive.

Joe Mullin, a patient of Cafaro's, is one of those desperate PWAs. "You name it, I've been on it," the 38-year-old former waiter says. Mullin's viral load had been down almost below the level blood tests can detect on a combination of AZT, 3TC, indinavir, saquinavir and delavirdine. Unlike many PWAs, Mullin says, "I never got much out of the protease inhibitors," and it took the five-drug regimen to keep his virus in check. But even that combination has begun to lose effectiveness and his viral load has rebounded to the anxiety-producing level of 140,000. "I needed 1592 yesterday," Mullin says, the worry obvious in his voice.

And Mullin is far from alone. Activist Linda Grinberg, president of her own AIDS research foundation and a board member of Project Inform, has been spearheading advocacy efforts around 1592. "I'm literally getting hundreds of calls from desperate patients, begging me to see if I can get them the drug," she says. "People who've failed all the existing drugs. The calls are just heartbreaking, people who are failing and losing hope."

Cafaro agrees. Asked how many patients she has who could benefit from 1592, she guesses, "a couple of hundred, I bet." Despite media hype last fall that virtually declared the epidemic over, she says, "people are still fighting for their lives. We have not reached any sort of situation where the end is near. We've stabilized some people, but some are getting resistant and getting worse." 1592, she notes, may be particularly valuable for people suffering AIDS-related dementia, because it penetrates the central nervous system far better than most anti-HIV drugs.

But few of Cafaro's patients, or anyone else's, are likely to get 1592 anytime soon, because what Glaxo has offered is a far cry from the large expanded access programs of yore. These programs, designed to provide PWAs running out of options with early, free access to promising new drugs while allowing manufacturers to collect data from large numbers of patients in real-world conditions, gave drugs like ddI, d4T and 3TC to tens of thousands of people prior to formal FDA approval.

But there has been no large-scale expanded access program since 3TC was distributed to some 30,000 PWAs in 1994 and 1995. Programs for the protease inhibitors have been minuscule: The indinavir and ritonavir expanded access programs are estimated to have reached only about 1,000 people each; the recent distribution of nelfinavir was a bit larger but still nowhere near the scale of the 3TC program.

Realizing the potential need for 1592, AIDS advocates began meeting with Glaxo last summer in an attempt to persuade the company to offer the drug immediately on a "compassionate use" basis to those in urgent need while gearing up for large-scale expanded access. There was rare unanimity among community leaders, with dozens of groups and 130 individual activists signing onto a consensus letter to the company demanding such an effort. Grinberg says the discussions were difficult and sometimes contentious but seemed for a while to be


PHOTO BY BOB GERNARTER

Martin Delaney

making progress. In a January conference call, she recalls, Glaxo representatives "said they were considering something soon, similar to what we'd proposed," and said they would file for FDA approval of the drug before the end of 1997.

TOO LITTLE, TOO LATE

But what Glaxo announced in a letter faxed to participants in the discussions April 28 was a major disappointment. It unveiled three programs—one for children, one for those suffering from "severe" AIDS dementia and a third for adults without dementia—which would enroll a total of 2,500 patients in all of North America, Europe and Australia. The pediatric program is set to begin in June, the others in July. Further, the company now doesn't expect to file for approval until mid-1998, and though it says it will begin a larger expanded access program early next year it has offered no specifics.

Another catch is that participants in the adult program, which presumably will be by far the largest, won't be able to go through their regular doctor but will have to enroll at one of an unspecified number of "geographically dispersed centers"—a departure from traditional procedure in expanded access. According to Glaxo spokesperson Kathy Bartlett, the list of centers won't be finalized for several weeks, but she expects "between 30 and 50 sites" worldwide.

Glaxo's announcement has drawn howls of outrage from AIDS activists across the country. When they got the news, Grinberg says, "Marty [Delaney, Project Inform's founder] and I went crazy. This thing is going to fill up in two weeks."

Even New York's Treatment Action Group, known for taking a cautious line on experimental drugs, is furious. "This program is far too little, far too late," comments Theo Smart, TAG's 1592 pointperson. "It's yet another example of how Glaxo doesn't have the best interests of people with AIDS at heart."

The company has given two reasons for not doing a large expanded access program now: Supply problems and a lack of adequate safety data. Glaxo has said that a manufacturing glitch with the adult formulation forced it to reformulate, crimping the supply.

But Bartlett insists the most important consideration is safety. "There's only been 250 people treated with 1592 to date, so we wanted to work with a small group of physicians and work with them to make the best decisions on the use of this drug," she explains. "We especially don't have a lot of data in [treatment] experienced patients... We also have a onsibility to collect meaningful data. That's what we're hearing from the community: Don't just throw the drugs out there.... We've had several meetings with the community. We've tried to be responsive to people's concerns, and we certainly heard loud and clear that people wanted us to collect meaningful data. It's a balancing act."

But AIDS activists aren't buying Glaxo's assertions. ACT UP/Golden Gate member Matthew Sharp, himself in urgent need of 1592 after becoming resistant to all the other nukes, argues, "As a PWA at this stage in the disease I don't have time to play around and wait until safety data comes forward. The company has no right to tell us we shouldn't take that risk."

And Baker notes, "In the history of expanded access and compassionate use there's never been a lot of safety data. That's just the nature of expanded access. And this drug doesn not give any indication of having severe side effects."

TAG has often called for better data on new drugs, but Smart says, "It's clear they're twisting our calls to collect meaningful data from compassionate use programs into an excuse to limit access. Glaxo Wellcome is the largest, richest pharmaceutical company in the world, has profited more from the AIDS crisis than anyone and clearly has the resources to develop novel programs to collect better data without limiting access."

And if supply is really a problem, the activists add, then Glaxo—whose 1996 pre-tax profits amounted to $4.77 billion—could easily hire an outside contractor to help produce the supplies needed.

MORE TROUBLE AHEAD?

Just as alarming to AIDS advocates as the 2,500-patient limit is the fact that access will be restricted to a relative handful of sites. Even if Glaxo goes for Bartlett's high-end figure of 50 centers and the U.S. gets half of them, that means only 25 locations in the entire country where participants will have to go to sign up and for periodic follow-up visits.

Names Project founder Cleve Jones thinks that means people in places like rural Sonoma County, where he now lives, will be left out. "It's going to be a situation where only those who've really learned to work the system will get this drug," he worries, and travel to San Francisco—likely to be the nearest site—will be "a big problem" for several friends in desperate need.

Jones, who has seen two friends do well in a 1592 trial and knows several others who urgently need the drug, thinks it is time for the community to mobilize. "There are people in the treatment activist community who think that Glaxo Wellcome is deliberately delaying development to maximize profits on AZT and 3TC," whose sales might decline if 1592 became available on a large scale, he notes. "I have not yet reached that conclusion, but it's getting harder and harder to forgive the delays. I've been an AIDS activist for 16 years and this is one of the most frustrating situations I've ever encountered," he declares. "The drug works and they know it. It's just stalling."

That sentiment seems just about unanimous among AIDS activists. ACT UP/Golden Gate has made 1592 an urgent priority and is developing a series of protest actions which it hopes to coordinate with other groups around the country. TAG is writing a new letter demanding a larger program which it will ask other groups to sign, and Smart hints that that is just the beginning. "I think Glaxo is going to come under strong attack from the community," he says. "Although the days of activism in the streets may appear to be over, there are a number of other ways the community may be able to hurt Glaxo Wellcome." ▼

GlaxoWellcome

June 6, 1997

Donna J. Freeman, M.D.
Acting Director, Division of Antiviral Drug Products
Food and Drug Administration, HFD-530
Attention: Document Control Room
9201 Corporate Boulevard
Fourth Floor
Rockville, MD 20850

RE: IND 45,331; 1592U89 Caplets;
Other: Letter of Authorization from Sponsor for Dr. Behrman;
Serial No.: 151

Dear Dr. Freeman:

Reference is made to a teleconference between Mr. Zeccola and Dr. Cocchetto on June 4, 1997, as well as a three-way teleconference between Mr. Anthony Zeccola, Mr. Daniel Montoya (Office of National AIDS Policy), and Dr. Cocchetto on June 5, 1997. In these teleconferences, we discussed the requests from Ms. Sandra Thurman (Director, Office of National AIDS Policy) for briefings on general aspects of antiretroviral drug development, as well as general information on the status of clinical development of 1592U89.

We appreciate Mr. Zeccola's effort to apprise Glaxo Wellcome of the requests from Ms. Thurman's Office, as well as his high level of attention to the confidentiality issues governing information in IND 45,331. Glaxo Wellcome continues to strive to sustain open and informative lines of communication with patient community groups and various governmental offices, including the Office of National AIDS Policy. Therefore, we are pleased to assist in this matter. During the teleconference of June 5, Dr. Cocchetto offerred that GW personnel are willing to participate in a three-way discussion among FDA's review team, members of the Office of National AIDS Policy, and GW. Mr. Montoya stated his preference to obtain a briefing from Dr. Rachel Behrman on general aspects of antiretroviral drug development, including some general information on the status of clinical development of 1592U89. Dr. Cocchetto agreed with Mr. Zeccola's recommendation that GW would supply a letter of authorization to FDA on the types of information that can be disclosed by Dr. Behrman. Our understanding is that Dr. Behrman will meet with Ms. Thurman on June 9.

Glaxo Wellcome Inc.
Five Moore Drive
PO Box 13398
Research Triangle Park
North Carolina 27709

Telephone
919 248 2100

It is acceptable to Glaxo Wellcome for Dr. Behrman to disclose the following information about 1592U89 to Ms. Thurman and Mr. Montoya:

- GW has completed its End-of-Phase II meeting with FDA. The results of Phase I and II studies provide encouraging results on antiviral activity and acceptable safety profile as the basis for proceeding to Phase III. Approximately 250 patients have been treated with 1592 to date.
- GW and FDA are communicating frequently and in detail regarding development of 1592. In addition, GW and FDA have consulted with the Antiviral Drugs Advisory Committee regarding this drug. GW believes that both GW and FDA have actively sought creative and innovative approaches to speed the development of 1592, while not diminishing the importance of attention to the safety of patients participating in clinical trials.
- The proposed Phase III protocols have been provided by GW to FDA, then subsequently reviewed, revised, and agreed with FDA. GW's understanding with FDA is that the Phase III protocols may be initiated. Enrollment of patients into Phase III studies has recently begun.
- GW has completed some of the most important drug-drug interaction studies, e.g., 1592/zidovudine and 1592/lamivudine. Additional studies will be done.
- With FDA's support, GW is pursuing concurrent development of 1592 for adults (via a tablet formulation) and pediatric patients (via a strawberry-banana flavored solution formulation). In view of very limited pediatric data on some other antiretroviral drugs, GW is very pleased to be able to pursue concurrent development in adults and pediatric patients.
- Concurrent with Phase III studies, GW is initiating an open-label "compassionate use program" as a means to provide 1592 to 2,500 patients with HIV who have few treatment options, while not competing for enrollment in Phase III studies. This compassionate use program will provide 1592 to three patient groups: (1) pediatric patients who have few treatment options, (2) adult patients who have few treatment options, and (3) patients with severe AIDS dementia complex. Future initiation of a traditional expanded access program will depend on accumulation of sufficient safety data to support such a program, as well as knowledge from Phase II and III studies about optimal therapeutic use of 1592.

Please note that Glaxo Wellcome's preference is that Dr. Behrman not discuss information about *Virology* (e.g., information on resistance), *Chemistry, Manufacturing, and Controls*, or *Nonclinical Pharmacology & Toxicology*. We prefer to be directly involved in discussions of these topics.

This submission is provided in quadruplicate. In addition, a copy was transmitted via FAX to Mr. Zeccola on June 6. Please contact Ms. Moore at (919)-483-9347 for any matters regarding this application. Thank you.

Sincerely,

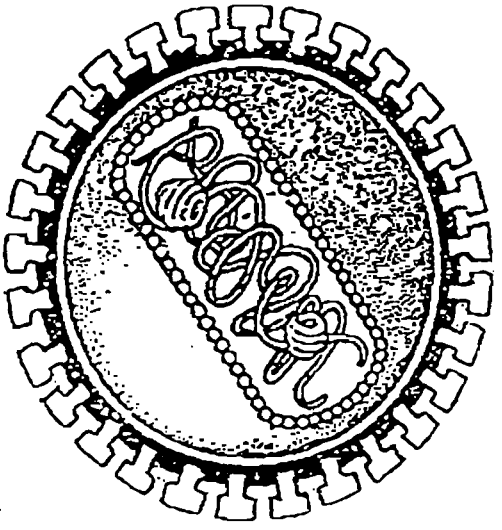
Martha Anne A. Moore David M. Cocchetto

Martha Anne A. Moore, R.Ph.
Product Director
Regulatory Affairs

David M. Cocchetto, Ph.D.
Director

Division of Antiviral Drug Products (DAVDP)
Office of Drug Evaluation IV
Center for Drug Evaluation and Research
Food and Drug Administration

TELEFACSIMILE TRANSMISSION RECORD



To: Daniel Montoya

FAX Number: 1-202-632-1096

Date: 6/9/97

Company:

Address:

No. pages (excluding cover): 3

Message: Here is a copy of the LOA that we received from Glaxo Wellcome

Resent / Last transmission appeared to be incomplete

From: Tony Zeccola

Telephone: (301) 827-2419

FAX Number: (301) 827-2523

Mail:

Division of Antiviral Drug Products
5600 Fishers Lane (HFD-530)
Rockville, Maryland 20857

Courier:

Division of Antiviral Drug Products
HFD-530
Document Control Room
9201 Corporate Blvd.
Rockville, Maryland 20850

FAX FAX FAX FAX

To : Dan Montoya

From: Jeff Getty

Date: May 30,1997

Thanks for setting up our call with Sandy on tues. June 3 at 3pm eastern. We will focus on 1592 concerns. Here is a list of the group so far.

1592 Access Working Group

Name	Number
Dr Andy Lipshits	516-938-5470 pf
Theo Smart TAG	212-260-2607 p 212-673-8921 f
Cleve Jones Names Project	707-865-9097 p 707-865-0541 f
John Iverson ACT UP East Bay	510-568-1680 pf
Jeff Getty ACT UP/Golden Gate	510-653-6278 p 510-653-6099 f
Kate Krauss Paul Davis ACT UP Phil.	215-731-1844 p 215-731-1845 f
Eileen Mitzmen Mother's Voc.	212-737-3335 p 212-737-1092 f
Linda Grinberg Ginberg Fd.	310-471-6565 p 310-471-4565 f
Bill Bauman ACT UP N.Y.	212-929-4952 pf
Matt Sharp ACT/UP Golden Gate	415-626-4053 p 415-626-0451 f
Ron Baker S.F AIDS Fd.	415-487-8065 p 415-487-8069 f
Sally Cooper PWA Health Gp.	212-255-0520 p 212-255-2080 f
Leigh Paidolfino-Danas UK	44-171-793-7444 p

FACTS ABOUT THE VACCINE RESEARCH CENTER AT THE NATIONAL INSTITUTES OF HEALTH

President Clinton announced on May 18, 1997 the creation of a new initiative to develop a vaccine against the AIDS virus within ten years. This initiative will be coordinated through the National Institutes of Health at a newly created Vaccine Research Center (VRC).

The President understands the critical importance of a comprehensive attack on the AIDS epidemic. His administration continues to strongly support current efforts to find a cure, to provide care and services for those already infected, and to stop the spread of HIV through prevention and education. The commitment to launch an aggressive AIDS vaccine initiative came at the request of AIDS activists, who were concerned that efforts to find a vaccine needed to be increased.

The President also appreciates the global implications of an AIDS vaccine. With most of the world's new AIDS cases located in impoverished areas, an AIDS vaccine is the only hope of stopping the global epidemic.

The VRC's role is primarily one of coordination, with some newly funded positions to augment current research work. These new positions will be paid for with NIH discretionary funds. Current NIH efforts to find a cure for those already infected and to treat AIDS-related illnesses will be unaffected (including work on therapeutic vaccines); no researcher positions or funding currently committed to this critical work will be used for vaccine research.

Some of the highlights of the Vaccine Reseach Center initiative are:

- The Vaccine Research Center will be a joint venture of the National Cancer Institute (NCI) and the National Institute of Allergy and Infectious Diseases (NIAID). They will begin by incorporating into the VRC a core of NIH scientists with interest and expertise in immunology, virology, and HIV vaccine research.

- The primary focus for the VRS will be to stimulate multidisciplinary research from basic and clinical immunology and virology through to vaccine design and production. It will integrate modern immunological science with a detailed understanding of the pathogenesis of HIV infection, development of immunogens and vectors, and new approaches to vaccination.

- The NCI and NIAID will provide physical, financial and human resources for the VRC. Funds for AIDS research are allocated according to the plans developed by the Office of AIDS Research (OAR) in consultation with the NIH Institutes. In fiscal year 1998, the OAR has proposed $10 million for the VRC, bring the total FY98 proposal for AIDS vaccine research to $150 million (a 33% increase over the past two years).

- At first, the VRC will be a "laboratory without walls," while laboratory space is sought in the vicinity of the NIH campus to bring the scientists together. Later, as scientists are recruited from outside the NIH ranks, NIH will consider constructing a building on the campus to house the VRC.

- A search committee will be named before the end of May to seek a scientist with specific expertise in vaccine development to be Director of the new VRC. There will be a broad, nationwide search.

Fax from Linda Grinberg

To: Sandy Thurmond	From : Linda Grinberg	
Company: The White House, AIDS Czar	Telephone: 310-471-6565	
Fax Number: 1-202-632-1096	Fax Number: 310-471-4565	
Subject :	Date: 5/16/97	Pages: 1

The address and phone number for Jennifer McMillan is as follows:

Glaxo Wellcome
5 Moore Drive
Research Triangle Park, NC 27709
(919) 483-2392

1592
ACT/3TC Placebo

Good luck! Hope you make some headway....

Thanks, again.

Linda

- Phase 2 has finished, phase 3 has begun
- Compassionate use —
- Criteria - Failed on all available treatments + aren't doing well
  * risks balanced with help
- 2500 - Centers will run trials, for monitoring
  2500 - Compassionate use
- expanded access — already

Fax from Linda Grinberg

To: Sandy Thurmond	From : Linda Grinberg	
Company: The White House, AIDS Czar	Telephone: 310-471-6565	
Fax Number: 1-202-632-1096	Fax Number: 310-471-4565	
Subject : 1592 Consensus Statement, etc.	Date: 5/16/97	Pages: 9

Thank you for getting back to me promptly on this urgent matter and your enthusiastic response.

As I stated, we've been meeting with various representatives of Glaxo since last Summer, but the chief liason to the community is Jennifer McMillan. Others in attendance at the various meetings and on the conference calls over the past year were Steve LeFon, who I believe is heading up the 1592 development program and Jim Rooney, head of clinical trials. The initial excitement regarding this drug dates back to January 1996, when their initial data was presented by Michael Saag, MD at the Retroviral Conference. Additional data was presented in Vancouver last July, which also created an even bigger buzz. The preliminary data presented at those conferences showed unprecedented antiviral activity for a drug of this class, a nucleoside drug or reverse trancriptase inhibitor (in the same class as AZT, 3TC, ddI, ddC, etc.) Glaxo had led everyone to believe until just recently they'd be filing for accelerated approval by the end of the year, but there have been unexplained delays...

I am quite literally being inundated with desperate phone calls and faxes now on a daily basis, and the frequency and utter desperation seem to be increasing. Many of these phone calls are gut wrenching and heartbreaking -- patients who have failed all the approved drugs with no other options on the horizon, with t-cells crashing and viral load soaring. Clearly many of these folks will not survive if they must wait until this drug is approved in Summer '98.

A program for 2,500 people worldwide (2,000 adults, 250 pediatric, 250 AIDS Dementia Complex) is just plain insulting and immoral, considering this is the largest pharmaceutical company in the world, which currently corners approximately 60-70% of the AIDS drug market (with AZT and 3TC). The "excuse" we are hearing is that there is a lack of safety data (only 250 patients studied thus far), however, any potential side effect of this drug cannot possibly outweigh the side effect of death for this late-stage population. Further, all the data presented thus far indicates that this is an extremely well-tolerated and safe drug. 1/3 Phase III don't come out

I am faxing herewith the original consensus statement that I began distributing in November, with the sign-ons as of 1/97. Hundreds of faxes have been received since January, so I need to spend a day updating that list of sign-ons. Additionally, the Wall St. Journal article will provide a bit more background info. Please feel free to call me if you have any questions or comments, anytime... It is so refreshing to see such an enthusiastic response. We sure need you in our corner... Thank you and I look forward to speaking with you next week.
Linda

Consensus Statement on 1592 Expanded Access and Accelerated Approval

- **Overview**

Access to Glaxo Wellcome's 1592U89 ("1592") now in development, potentially represents the only viable option for delaying disease progression for many people living with HIV and AIDS who have exhausted the benefit from currently approved antiviral therapies. In early clinical studies, 1592 has demonstrated a more potent level of antiviral activity than other RT inhibitors, with minimal side effects. It's most important property, however, is that people have not previously been exposed to it and it therefore offers the hope of renewed antiviral activity. This renders the drug critically important to two patient populations: (1) those who have already lost sensitivity to the other drugs of this type, and (2) those who need to use at least one "fresh" or new nucleoside analogue RT inhibitor to make reasonable use of combination therapy with protease inhibitors or non-nucleoside RT inhibitors. Existing evidence clearly suggests that combining such drugs with previously used therapies diminishes their effectiveness and leads to more rapid development of resistance.

The benefit of this drug may be limited due to the development of resistance, a problem common to all currently approved antiviral compounds. While it may take years of additional study to determine its optimal use, this should not delay prompt access to this therapy by people in immediate need. Delaying the availability of this drug until Phase III trials are fully accrued is unacceptable and represents a significant change from past practices. For example, the ddI, d4T, and AZT expanded access programs all took place while trials were still recruiting. We are very concerned that the recent activities of several pharmaceutical companies represents a broad effort to minimize the number of patients served by expanded access programs. Any such effort around 1592 would be a moral affront to the rights and needs of people with HIV/AIDS and their healthcare providers.

We hereby propose the following 1592 expanded access program, to be phased in in stages, with immediate access to those in urgent need.

- **First Phase - Compassionate Use/Salvage Therapy**

Glaxo Wellcome and the Food and Drug Administration must cooperate and take a more compassionate stance to make this promising compound immediately available in a "salvage program" once a recommended dosing schedule has been established. This compassionate access/salvage program should make drug available as soon as possible for those people who have failed existing therapies and risk near-term danger of death or life-threatening infections.

The development of this drug must take into consideration its unique potential to provide benefit to the acutely compromised segment of the HIV-infected population. Availability of salvage strategies is of the highest priority for people living with HIV. There is no logical or moral reason to withhold this drug from people with advanced illness, people whose lives hang in the balance. Currently, this compound qualifies, by any humane standard, for compassionate use.

This first phase of Compassionate Use/Salvage Therapy should provide 1592 without delay to patients who meet any one of the following two requirements:

1. ***CD4+ Cell Count <50 OR Viral Load >40,000 copies/ml AND Treatment Failure to approved RT Inhibitors AND at least one Protease Inhibitor;***
2. ***Diagnosis of AIDS Dementia Complex (ADC), unresponsive to existing therapies.***

We believe evidence of the above conditions can be accomplished with a minimal amount of paperwork. A physician's letter accompanied by one lab report should be sufficient to establish any of the above criteria.

- **Second Phase - Expanded Access**

This second phase of Expanded Access should provide 1592 during recruitment and conduct of Phase II/III clinical trials, but no later than ninety (90) days from the start-up of the First Phase, to patients who meet any of the following criteria:

1. ***Patients who do not qualify for or are denied entry in a 1592 clinical trial and have a medical need for 1592, or***

2. ***Patients who do not live within a radius of 15 miles of an active clinical trial site, or***
3. ***Patients whose lives would be immediately jeopardized by randomization to an ineffective treatment regimen, or***
4. ***Patients with a CD4+ Cell count below entry requirements of clinical trials, or***
5. ***Viral Load greater than 20,000 copies/ml., despite use of currently approved therapies, or***
6. ***Treatment Failure or demonstrated genotypic or phenotypic resistance to approved RT inhibitors.***

- **Accelerated Approval**

This compound should be licensed for accelerated approval as soon as possible. FDA approval of this compound should be based on existing regulations governing accelerated approval of new drugs for life-threatening illnesses:

1. ***Clear evidence of benefit on surrogate markers have been demonstrated;***
2. ***Principal toxicities and drug interactions have been defined;***
3. ***Longer-term development plans have been initiated designed to determine the drug's usefulness in promoting clinical and survival improvements and durability of response, as part of a medical strategy for coping with HIV infection.***

****We urge the sponsor to file applications for accelerated approval as soon as possible.***

- **Resistance, Pharmacokinetics and Drug Interactions**

As with all antivirals, the development of drug-resistant strains of virus, drug interactions and pharmocokinetic variances while using this compound may warrant additional considerations. To address this concern, sponsors should also be required, prior to accelerated approval, to present meaningful data on:

1. ***the speed and levels of resistance encountered;***
2. ***the degree of cross-resistance found with other nucleoside analogues;***
3. ***the interaction of the compound with other commonly used anti-HIV medications;***
4. ***bioavailability in men, women, and children and determination of the degree which blood levels vary depending on body weight.***

- **Summation**

Any effort to withhold access to promising compounds is contrary to the interests of HIV-infected people, inconsistent with the Accelerated Approval regulations, and scientifically unwarranted. The long history of the development of the earlier generation of antiviral drugs clearly demonstrates that it is possible to accrue patients and continue conducting clinical trials of compounds, long after their marketing approval. Because of the issues of drug resistance and drug failure over time, new therapies for HIV disease will continue to play a critical role no matter how many drugs become available on the market. New therapies, like 1592, must continue to be made available as rapidly as possible to patients with immediate needs for changed or improved treatment.

AGREED and ACCEPTED this ____ day of _____, 1996:
* *Revised as of 11/27/96*

By: _____ Of: _____

Signature **Organization**

Print Name: _____ **Please fax to: 310-471-4565**

ORGANIZATIONS: **SIGN-ONS AS OF JANUARY 25, 1997**

1. ACTUP BOSTON, Boston, MA
2. ACTUP EAST BAY, Oakland, CA
3. ACTUP GOLDEN GATE, San Francisco, CA
4. ACTUP LOS ANGELES, Los Angeles, CA
5. ACTUP NEW YORK, New York, NY
6. ACTUP PARIS, Paris, FRANCE
7. ACTUP PHILADELPHIA, Philadelphia, PA
8. AIDS ACTION COMMITTEE - BOSTON, Boston, MA
9. AIDS ACTION COUNCIL, Washington, DC
10. AIDS HEALTHCARE FOUNDATION, Pasadena, CA
11. AIDS PROJECT LOS ANGELES /APLA, Los Angeles, CA
12. AIDS RESEARCH ALLIANCE, Los Angeles, CA
13. AIDS RESEARCH INFORMATION CENTER, INC./ARIC, Baltimore, MD
14. AIDS SERVICE CENTER, Pasadena, CA
15. AIDS SURVIVAL PROJECT, Atlanta, GA
16. AIDS TREATMENT INITIATIVES, Atlanta, GA
17. AIDS TREATMENT NEWS, San Francisco, CA
18. BEING ALIVE, Los Angeles, CA
19. BRITISH COLUMBIA PERSONS WITH AIDS SOCIETY, Canada
20. CENTER FOR AIDS, THE, Houston, Texas
21. COUNSELING CENTER, THE dba GULF COAST MENTAL HEALTH, MI
22. FLORIDA AIDS ACTION COUNCIL, Florida
23. GAY MEN'S HEALTH CRISIS/GMHC, New York, NY
24. LINDA GRINBERG FOUNDATION, Los Angeles, CA
25. HOMESTEAD HOSPICE & THE "DALLAS HOUSE", Los Angeles, CA
26. IHS AT HANOVER
27. ISRAEL AIDS TASK FORCE, Tel Aviv, Israel
28. KRAUS MEDICAL PARTNERS, Los Angeles, CA
29. LAMBDA COUNSELING CENTER, Miami, Miami Beach, Ft. Lauderdale & Palm Beach, FL
30. LIVING WELL PROJECT/ASIAN PACIFIC ISLANDERS AIDS SERVICES, San Francisco, CA
31. LOG CABIN REBUBLICANS, Washington, D.C.
32. MOTHER'S VOICES, New York, NY
33. MULTICULTURAL AIDS COALITION, INC., Boston, MA
34. NATIONAL AIDS TREATMENT ADVOCACY PROJECT/NATAP, New York, NY
35. NATIONAL ASSOCIATION OF PEOPLE WITH AIDS/NAPWA, Washington, DC
36. NATIONAL MINORITY AIDS COUNCIL, Washingto, DC
37. OPEN DOORS
38. PARAGON MEDICAL RESEARCH, Los Angeles, CA
39. POZ MAGAZINE, New York, NY
40. PROJECT INFORM, San Francisco, CA
41. PROJEKT INFORMATION, Munich, Germany
42. PWA HEALTH GROUP, New York, NY
43. PWAlive/MINNESOTA, Minneapolis, MN
44. REACH OF SOUTHERN ARIZONA, AZ
45. RESEARCH SANCTUARY, Los Angeles, CA
46. SAN FRANCISCO AIDS FOUNDATION/BETA, San Francisco, CA
47. SAN LUIS OBISPO HIV CARE CONSORTIUM, CA
48. SEARCH FOR A CURE, Boston, MA
49. SO. MISSISSIPPI AIDS TASK FORCE, MI
50. TEST POSITIVE AWARE, Chicago, IL
51. TREASURE COAST COMMUNITY AIDS NETWORK, Florida
52. TREATMENT ACTION GROUP/TAG, New York, NY
53. TREATMENT & DATA COMMITTEE, New York, NY
54. UNITED FOUNDATION FOR AIDS, Miami, FL
55. WOMEN ALIVE, Los Angeles, CA

INDIVIDUALS: SIGN-ONS AS OFJANUARY 16, 1997

1. Linda R. Allen
2. Moises Agosto, National Minority AIDS Council, Washington, DC
3 Alberto Avendano, MD, Florida AIDS Action Council, FL
4. Bill Bahlman, Treatment & Data Committee, NY
5. Cornelius Baker, National Association of People with AIDS/NAPWA, Washington, DC
6. Ron Baker, SF AIDS Foundation/BETA, San Francisco, CA
7. David Barr, Gay Men's Health Crisis/GMHC, New York, NY
8. Dirk Belau, Geneva, Switzerland
9. Carol Bennett
10. Jessica C. Bigg, So. Mississippi AIDS Task Force
11. Voa Bigg, So. Mississippi AIDS Task Force
12. G'dali Braverman, Living Well Project, San Francisco, CA
13. William K. Brent, Jr., So. Mississippi AIDS Task Force
14. Larry Bresslour, Search for a Cure, Boston, MA
15. Gregory Britt, AIDS Research Alliance, Los Angeles, CA
16. Sara J. Brookins, So. Mississippi AIDS Task Force, Biloxi, MI
17. Nicholas F. Brookins, So. Mississippi AIDS Task Force, Biloxi, MI
18. Carl Brown, Treasure Coast Community AIDS Network, FL
19. Glenn Brown, ACTUP Philadelphia, PA
20. William D. Bryant, Boulder Creek, CA
21. Todd Burger, Chicago, IL
22. Jan Casey
23. Jeffrey B. Cason, New York, NY
24 Peter Cashman, ACTUP Los Angeles, CA
25. Henry E. Chang, AIDS Healthcare Foundation, CA
26. James Clark, Laguna Beach, CA
27 Mark Cohen, United Foundation for AIDS, So. Miami, FL
28. Richard Cooper, M.D., Kraus Medical Partners, Los Angeles, CA
29. Sarah ("Sally") C. Cooper, PWA Health Group, New York, NY
30. Jim Corti, Research Sanctuary & Linda Grinberg Foundation, Los Angeles, CA
31. Mark Cohen, United Foundation for AIDS, Miami, FL
32. Gary E. Costa, Being Alive, CA
33. John Curtis Cottingham, AL
34. Linda F. Cottingham, State of Alabama, Dept. of Human Resources
35 Spencer Cox, Treatment Action Group/TAG, New York, NY
36. Myron C. Crider, Morrow, GA
37. Donald T. Daniels, PAC, AIDS Healthcare Foundation, Los Angeles, CA
38. Robert Dal Porto, PWA with Being Alive, Los Angeles, CA
39 Kenneth De Haan
40. Martin Delaney, Project Inform, CA
41. Rebecca Dennison, W.O.R.L.D., Oakland, CA
42. John Deshane, Los Angeles, CA
43. Scott Dewees, W. Hollywood, CA
44. John Dolan, Raleigh, N.C.
45 Jim Driscoll, Log Cabin Republicans, San Francisco, CA
46. Marianne DuBose, So. Mississippi AIDS Task Force
47. Ferd Eggan, AIDS Coordinator, City of Los Angeles, CA
48. Peter Engelhard, D.O., Fisher Medical Group, Miami, FL
49. Charles Farthing, M.D., AIDS Healthcare Foundation, Los Angeles, CA
50. Tracy Fennell
51. Gil Ferguson, British Columbia Persons with AIDS Society, Canada
52. Brenda Freiberg, Board of Directors, Project Inform & AIDS Service Center, CA
53. Ruben Gamundi, AIDS Project Los Angeles, CA
54. Ramon M. Garcia, REACH of So. Arizona, Bisbee, Arizona
55. Aileen Getty, Homestead House & The "Dallas House", Los Angeles, CA
56. Jeff Getty, ACT UP Golden Gate, San Francisco, CA
57 Joseph L. Goebelt, Santa Clara, CA
58. Michael Gottlieb, M.D., Gottlieb Medical Group, Los Angeles, CA
59. Jeff Graham, AIDS Survival Project, Atlanta, GA
60. Linda Grinberg, Linda Grinberg Foundation & Project Inform, CA
61. John Haiduck, Test Positive Aware, Chicago, IL

62. Lee Hardy, ARIC, Inc., Baltimore, MD
63. Larry Harman, Ph.D., Lambda Counseling Center, Miami, Ft. Lauderdale & Palm Beach, FL
64. Zaida Harrington, Biloxi, MI
65. Rene Milet Hernandez, Multicultural AIDS Coalition, Inc., Boston
66. Rachel Hincey
67. Gideon Hirsch, Israel AIDS Task Force, Tel Aviv, Israel
68. Peter M. Hoffman, Treasure Coast Community AIDS Network, FL
69. Carlton Hogan, PWAlive, Minneapolis, Minnesota
70. Ernest Hopkins, National Association of People with AIDS/NAPWA, Washington, DC
71. Dennis Hughes, Treasure Coast Community AIDS Network, FL
72. Terrence L. Ibbs, D.O., N. Miami Beach, FL
73. Crystal Iondan, Treasure Coast Community AIDS Network, FL
74. John Iverson, ACTUP/East Bay, Oakland, CA
75. John S. James, AIDS Treatment News, San Francisco, CA
76. Joseph J. Johnson, Treasure Coast Community AIDS Network, FL
77. Robert Folan Johnson, ACTUP Boston, Boston, MA
78. Cleve Jones, Founder/AIDS Memorial Quilt
79. Larry Kessler, AIDS Action Committee - Boston, Boston, MA
80. Chai Khoo, San Jose, CA
81 David E. Kilburn, San Luis Obispo HIV Care Consortium, CA
82. Barry Krost, Board of Directors, Project Inform, San Francisco, CA
83. Ann Kurth, Mother's Voices, NY
84. Terry Laug, San Jose, CA
85. James Learned, PWA Health Group, New York, NY
86. Gina Lee, Gahanna, Ohio
87. Sheryl A. Leon, The Counseling Center dba Gulf Coast Mental Health, Mississippi
88. Jules Levin, National AIDS Treatment Advocacy Project/NATAP, NY
89. Dennis Littrell, Raleigh, N.C.
90. Mary Lucey, AIDS Policy Analyst, City of Los Angeles
91. Nancy MacNeil, Project Director, Women Alive, Los Angeles, CA
92. James V. Madaras, Treasure Coast Community AIDS Network, FL
93. Thomas L. Magee, M.D., Medical Offices, Los Angeles, CA
94. Rachelle Mark, Los Angeles, CA
95. Joel Martinez, The Center for AIDS, Houston, Texas
96. James McKee
97. Paul McLaughlin, Treasure Coast Community AIDS Network, FL
98. Robin Capps Munger
99. Christopher B. O'Hare, Treasure Coast Community AIDS Network, FL
100. John Ortado, Jr., Treasure Coast Community AIDS Network, FL
101. Paula L. Osborn
102. Robin R. Pabon, So. Mississippi AIDS Task Force
103. Shirley Paugh, Treasure Coast Community AIDS Network, FL
104 Tony Poleto, Treasure Coast Community AIDS Network, FL
105. Wallace Potts, self-employed film archivist, Los Angeles, CA
106. Chris Presley
107. Robert Rivera, So. Mississippi AIDS Task Force
108. Nicholas Roche, ACTUP Paris, Paris, FRANCE
109. Gary R. Rose, AIDS Action Council, Washington, DC
110. James Rousey, Exec. Director, AIDS Treatment Initiatives, Atlanta, CA
111. Maria L. Samies, So. Mississippi AIDS Task Force
112. John B. Schulz, Los Angeles, CA
113. Sue W. Scott, AIDS Service Center, Pasadena, CA
114. Matthew Sharp, ACTUP Golden Gate, San Francisco, CA
115. Michael Shriver, NAPWA, Washington, D.C.
116. John E. Smith, Treasure Coast Community AIDS Network, FL
117. William L. Snedden, Treasure Coast Community AIDS Network, FL
118 Andrea Springsteen, Los Angeles, CA
119 David Springsteen, Los Angeles, CA
120. Judy Springsteen, Los Angeles, CA
121 Lois Springsteen, Boulder Creek, CA
122. Wayne P. Springsteen, Los Angeles, CA
123 Joe M Stewart
124. Norm Stuart, Research Sanctuary, Los Angeles, CA

125. Sean Strub, Poz Magazine, New York, N.Y.
126. Richard Tafel, Log Cabin Republicans, Washington, DC
127. Rob Tan, Rob Tan & Associates, San Francisco, CA
128. Susanna Calvin Thomas, Open Doors
129. Delia A. Viator, The Counseling Center dba Gulf Coast Mental Health, Biloxi, Mississippi
130. Gerald S. Viator, Biloxi, Mississippi
131 Oswald T. Weber, Founding Director, Projekt Information, Munich, Germany
132. Leland J. Weseal, Treasure Coast Community AIDS Network, FL
133. Robert C. White, St. Louis, Missouri
134. Mark Williams, PWA, New Jersey
135. Lee Winchell, Los Angeles, CA
136. Phillip Winchell, APLA client, Los Angeles, CA
137. Yvonne Wind, PA-C, N. Miami Beach, FL
138. Vicki Worley, IHS, Hanover

11/12/96 Why Isn't Glaxo's New AIDS Drug Ready Yet?
By Michael Waldholz
Staff Reporter of The Wall Street Journal

Stephen Gendin is falling behind in his race against AIDS. He has staved off illness for more than a decade by aggressively cycling through a battery of medications, turning to a new drug each time the virus mutated and overcame an earlier one. "I've taken AZT, DDC, DDI, D4T, 3TC, Saquinavir, Norvir," says Mr. Gendin, the 30-year-old co-founder of a New York mail-order drug company.

"Now I need what's next," he says "1592 is next." But the potent drug 1592 has been stuck in Glaxo Wellcome PLC's research pipeline for seven years. It now seems unlikely that it will hit the market before mid-1998.

What's taking so long? Glaxo says it didn't recognize the drug's power until recently and now is moving as quickly as it can to complete necessary safety trials and make the drug available. But some critics believe the company is dragging out the development of 1592. After all, development of the powerful AIDS drugs known as protease inhibitors began less than five years ago, and those drugs have been available for almost a year now, extending the lives of thousands of people. The controversy reflects the tremendous demand for new AIDS drugs now that it appears the disease responds, at least temporarily, to treatment.

AIDS activists charge that Glaxo is trying to protect the sales of its two older AIDS drugs, AZT and 3TC. Their combined revenue is expected to hit $600 million this year, double the total in 1995, and could exceed $1 billion in two years. Sales are booming as patients adopt a "cocktail" regimen that combines the two older drugs with one of the new protease inhibitors.

But 1592 is 10 times more powerful than AZT, its chemical and corporate cousin, and it avoids AZT's dangerous side-effects. "Who's going to take AZT if 1592 is available?" asks Martin Delaney, founding director at Project Inform, an AIDS advocacy group

At the very least, Mr. Delaney and many other AIDS activists contend, Glaxo should make 1592 available immediately to thousands of desperately ill patients under a "compassionate access" program while the drug winds through the long approval process. Virtually every other new AIDS drug has taken that route.

Glaxo officials, saying they haven't gathered enough safety data to do that, deny that they have put commercial considerations before compassion. They concede that work on 1592 and other drugs languished amid the distractions of Glaxo's $14.8 billion acquisition of Wellcome PLC last year. Except for 3TC, all the AIDS drugs in the works were from the Wellcome side Once Glaxo took over, it didn't offer comparable jobs to most of the top Wellcome research managers who had shepherded
1592 through initial studies. As a result, most of the managers left.

"There were a lot of distractions," says James Rooney, who ran a clinical-studies department at Wellcome before the merger and is now a vice president at Gilead Sciences Inc., Foster City,
Calif. "There was a lot of wrestling over new procedures, switching jobs and locations, and uncertainty over which projects would go forward," he says.

The drug 1592 was one of a batch of new chemicals developed in the labs at Wellcome in the late 1980s, when scientists were looking for better versions of AZT. Both drugs, as well as 3TC, belong to a class called nucleosides, which work by blocking an enzyme that is critical to an early phase in the replication of HIV, the virus that causes AIDS.

11/12/96 Why Isn't Glaxo's -2-: In Second Clinical Trial Phase

Wellcome researchers spent several years testing other compounds first. "We had no reason to expect 1592 to be so much more powerful than the others," says Lynn Smiley, director of the
company's AIDS clinical trials. Scientists uncovered 1592's antiviral muscle about a year ago, after another experimental drug failed and they began human testing of 1592.

The drug is now in the second of three phases of clinical trials. Glaxo officials say they need another year or more before seeking Food and Drug Administration approval. Because 1592 will be combined with so many other medicines as part of the "cocktail" therapy -- about nine other AIDS drugs are
approved or soon will be -- the company must conduct a wider range of safety trials than its earlier drugs required

"We are very sensitive to the desperation out there from patients who need new drugs," says Stephen LaFon, a Glaxo researcher who helps run tests of the drug. "But we have to balance speed of getting the drug to these few patients and the need to get the best kind of clinical information we can."

That doesn't help patients who have already developed resistance to AZT and other nucleosides. The cocktail approach, by combining three or more drugs that attack different parts of the virus, has been able to reduce HIV to undetectable levels in many patients, allowing the immune system to rebound and fight off deadly infections. But if a patient's HIV has already developed resistance to the AZT-like component, the cocktail will ultimately fail. 1592 could be the new ingredient that would make the cocktail work again.

"You can't just pile a protease drug atop a failing regimen. It won't work," says Martin Markowitz, a research physician at the Aaron Diamond AIDS Research Center in New York.

Demands for the release of 1592 have been growing steadily since this past summer, when Glaxo scientists revealed results of a three-month-long, 80-person study that showed that combining 1592 and AZT was as effective at reducing HIV levels as some three-drug cocktails that included a protease inhibitor. Patient advocates argue that several drugs were released for "compassionate access" based on even fewer test patients than Glaxo has used in studying 1592. But Glaxo officials say the manufacturing process isn't geared up enough to support widespread distribution right now. Jennifer McMillan, a Glaxo executive who works with AIDS activists, also cites more serious concerns: If 1592 were released now, patients might be less willing to participate in clinical trials because
they could, instead, get easy access to free doses of the drug.

Glaxo, surprised by surging demand for 3TC after studies underscored its power, had let 30,000 patients get that drug in a similar program from 1993 to 1995, but it was unable to collect much useful data. "We want to be careful and not repeat that mistake," Ms. McMillan says.

That distresses some people struggling against infection. Spencer Cox, who helps run Treatment Action Group, a New York advocacy group, has watched the HIV levels in his blood rise sharply in recent months as older drugs stopped working and new protease drugs couldn't plug the gap. "I fully understand Glaxo Wellcome's desire for caution," he says. "But I also know I could benefit from 1592 right now. I don't see any reason not to make it available today."

11/12/96 Why Isn't Glaxo's -3-: Only 175 Patients Have Taken Drug

For now, only 175 patients have taken 1592, and only several hundred more will get it when final-stage trials begin sometime next year. That leaves out patients like Mr. Gendin, the 30-year-old New Yorker. He can't take part in Glaxo's expanded trials because such experiments typically use subjects who haven't already developed resistance to earlier drugs. His virus levels have more than doubled in recent months, and Mr. Gendin worries more about HIV outracing his immune system than about
any safety problems of Glaxo's experimental drug.

"I have to have" 1592, Mr. Gendin says simply "I've got nothing to lose."

From Discovery to Approval

Glaxo Wellcome's new AIDS drug is taking longer to become
available than some recently developed AIDS drugs

DRUG	*COMPANY*	*DISCOVERED*	*TIME TO APPROVAL*
1592	**Glaxo Wellcome**	**1989**	**About nine years***
Invirase	Hoffmann-La Roche	1989	Six years
Crixivan	Merck	1992	Four years
Norvir	Abbott Labs	1993	Three years
141	Glaxo Wellcome (Vertex)	1993	Five years*
Viracept	Agouron Pharmaceuticals	1994	Three years*

*Anticipated

CNBC —

Cleve — Sonoma — rural county Last week
Eileen — Mothers Voices
There are no side effects worse than death
Bill Bowman — Act up NY
P02 expo,
Marty Delany —
end of the year production
* small scale production can be done
Ron Baker —
People are still dying with drugs available
Kate Kraus —
No protocol for Drug Companies to get drugs to market quickly + expanded access program + compassionate use
John Iversen — ACT UP E. Bay
Spoke to Glaxo + they are clearly stalled
Linda Cringberg —
Get Glaxo to make some good faith effort
- some statement
Jules
Commitment from Glaxo to be flexible and to be creative in their production
Act up Golden Gate —
Mathew Jeff — FDA is very willing to work with us — [redacted]
Safety — viral load into —
— Should be able to approve by fall under accelerated approval
Patient on AZT about to run out

Action — Expand Protocol

CNBC —
Glaxo —
Burroughs Wellcome —

What is FDA doing?
Why nine years?

~~If any~~

What has our experience been with Class III in the past?

Bruce Mirken
829 Hayes St. #1
San Francisco, CA 94117
Tel (415)621-8258
Fax (415)552-7170

Sandy Thurman
Office of National AIDS Policy
(202)632-1096

5/18/97

Dear Ms. Thurman,

Cleve Jones asked me to send you a copy of this article, which concerns the availability (or lack thereof) of an extremely important new antiretroviral drug. I hope you find it useful.

Sincerely,

Bruce Mirken

P.S. I'm sorry we didn't manage to connect while you were in San Francisco. Though my immediate deadline has obviously passed, I hope we can arrange an interview the next time you visit the West Coast.

The Fight for 1592

AIDS Activists Battle Glaxo over Access To Anxiously Awaited New Drug

PHOTO BY MARC GELLER

Cleve Jones

PHOTO BY BRUCE MIRKEN

Matthew Sharp

PHOTO BY RICK GERHARTER

Martin Delaney

BY BRUCE MIRKEN

A decade after the high price of AZT caused AIDS activists to declare war on Burroughs Wellcome, the AIDS community is again gearing up for battle with the pharmaceutical giant—now known as Glaxo Wellcome—over access to what San Francisco AIDS Foundation director of treatment education and advocacy Ron Baker has called "the most important AIDS drug in the research pipeline."

That drug, known by the code name 1592U89 and commonly referred to simply as 1592, belongs to the class of drugs called nucleoside analogs, the same category as AZT, 3TC, ddC, ddI and d4T. In an article published last December Baker called it "the only nucleoside analog in the research pipeline that appears safe and potent." In early tests 1592 has demonstrated far more anti-HIV punch than any of the earlier "nukes," and appears to be less toxic as well. In one study of 1592 combined with AZT, the two-drug combination reduced HIV blood levels by as much as 99 percent in 29 volunteers, far better than any 2-nuke combination ever tested.

The company has responded to pleas for access to the drug with a tiny program that San Francisco AIDS specialist Dr. Virginia Cafaro dismisses as "pathetic," but which Glaxo insists is all it can do for now.

DESPERATE PATIENTS

While another nuke may seem like small potatoes in the age of protease inhibitors, the protease drugs, along with the recently approved non-nucleoside reverse transcriptase inhibitors nevirapine and delavirdine, must be combined with other drugs to get their full effect. The nukes are a key ingredient of these combination regimens; but plenty of people with AIDS have used up all of the older nukes, the HIV in their bodies gradually having become resistant to each of the drugs. For them 1592 represents the only hope for building a drug cocktail that can keep them alive.

Joe Mullin, a patient of Cafaro's, is one of those desperate PWAs. "You name it, I've been on it," the 38-year-old former waiter says. Mullin's viral load had been down almost below the level blood tests can detect on a combination of AZT, 3TC, indinavir, saquinavir and delavirdine. Unlike many PWAs, Mullin says, "I never got much out of the protease inhibitors," and it took the five-drug regimen to keep his virus in check. But even that combination has begun to lose effectiveness and his viral load has rebounded to the anxiety-producing level of 140,000. "I needed 1592 yesterday," Mullin says, the worry obvious in his voice.

And Mullin is far from alone. Activist Linda Grinberg, president of her own AIDS research foundation and a board member of Project Inform, has been spearheading advocacy efforts around 1592. "I'm literally getting hundreds of calls from desperate patients, begging me to see if I can get them the drug," she says. "People who've failed all the existing drugs. The calls are just heartbreaking, people who are failing and losing hope."

Cafaro agrees. Asked how many patients she has who could benefit from 1592, she guesses, "a couple of hundred, I bet." Despite media hype last fall that virtually declared the epidemic over, she says, "people are still fighting for their lives. We have not reached any sort of situation where the end is near. We've stabilized some people, but some are getting resistant and getting worse." 1592, she notes, may be particularly valuable for people suffering AIDS-related dementia, because it penetrates the central nervous system far better than most anti-HIV drugs.

But few of Cafaro's patients, or anyone else's, are likely to get 1592 anytime soon, because what Glaxo has offered is a far cry from the large expanded access programs of yore. These programs, designed to provide PWAs running out of options with early, free access to promising new drugs while allowing manufacturers to collect data from large numbers of patients in real-world conditions, gave drugs like ddI, d4T and 3TC to tens of thousands of people prior to formal FDA approval.

But there has been no large-scale expanded access program since 3TC was distributed to some 30,000 PWAs in 1994 and 1995. Programs for the protease inhibitors have been minuscule: The indinavir and ritonavir expanded access programs are estimated to have reached only about 1,000 people each; the recent distribution of nelfinavir was a bit larger but still nowhere near the scale of the 3TC program.

Realizing the potential need for 1592, AIDS advocates began meeting with Glaxo last summer in an attempt to persuade the company to offer the drug immediately on a "compassionate use" basis to those in urgent need while gearing up for large-scale expanded access. There was rare unanimity among community leaders, with dozens of groups and 130 individual activists signing onto a consensus letter to the company demanding such an effort. Grinberg says the discussions were difficult and sometimes contentious but seemed for a while to be making progress. In a January conference call, she recalls, Glaxo representatives "said they were considering something soon, similar to what we'd proposed," and said they would file for FDA approval of the drug before the end of 1997.

TOO LITTLE, TOO LATE

But what Glaxo announced in a letter faxed to participants in the discussions April 28 was a major disappointment. It unveiled three programs—one for children, one for those suffering from "severe" AIDS dementia and a third for adults without dementia—which would enroll a total of 2,500 patients in all of North America, Europe and Australia. The pediatric program is set to begin in June, the others in July. Further, the company now doesn't expect to file for approval until mid-1998, and though it says it will begin a larger expanded access program early next year it has offered no specifics.

Another catch is that participants in the adult program, which presumably will be by far the largest, won't be able to go through their regular doctor but will have to enroll at one of an unspecified number of "geographically dispersed centers"—a departure from traditional procedure in expanded access. According to Glaxo spokesperson Kathy Bartlett, the list of centers won't be finalized for several weeks, but she expects "between 30 and 50 sites" worldwide.

Glaxo's announcement has drawn howls of outrage from AIDS activists across the country. When they got the news, Grinberg says, "Marty [Delaney, Project Inform's founder] and I went crazy. This thing is going to fill up in two weeks."

Even New York's Treatment Action Group, known for taking a cautious line on experimental drugs, is furious. "This program is far too little, far too late," comments Theo Smart, TAG's 1592 pointperson. "It's yet another example of how Glaxo doesn't have the best interests of people with AIDS at heart."

The company has given two reasons for not doing a large expanded access program now: Supply problems and a lack of adequate safety data. Glaxo has said that a manufacturing glitch with the adult formulation forced it to reformulate, crimping the supply.

But Bartlett insists the most important consideration is safety. "There's only been 250 people treated with 1592 to date, so we wanted to work with a small group of physicians and work with them to make the best decisions on the use of this drug," she explains. "We especially don't have a lot of data in [treatment] experienced patients... We also have a responsibility to collect meaningful . That's what we're hearing from the community: Don't just throw the drugs out there.... We've had several meetings with the community. We've tried to be responsive to people's concerns, and we certainly heard loud and clear that people wanted us to collect meaningful data. It's a balancing act."

But AIDS activists aren't buying Glaxo's assertions. ACT UP/Golden Gate member Matthew Sharp, himself in urgent need of 1592 after becoming resistant to all the other nukes, argues, "As a PWA at this stage in the disease I don't have time to play around and wait until safety data comes forward. The company has no right to tell us we shouldn't take that risk."

And Baker notes, "In the history of expanded access and compassionate use there's never been a lot of safety data. That's just the nature of expanded access. And this drug doesn't not give any indication of having severe side effects."

TAG has often called for better data on new drugs, but Smart says, "It's clear they're twisting our calls to collect meaningful data from compassionate use programs into an excuse to limit access. Glaxo Wellcome is the largest, richest pharmaceutical company in the world, has profited more from the AIDS crisis than anyone and clearly has the resources to develop novel programs to collect better data without limiting access."

And if supply is really a problem, the activists add, then Glaxo—whose 1996 pre-tax profits amounted to $4.77 billion—could easily hire an outside contractor to help produce the supplies needed.

MORE TROUBLE AHEAD?

Just as alarming to AIDS advocates as the 2,500-patient limit is the fact that access will be restricted to a relative handful of sites. Even if Glaxo goes for Bartlett's high-end figure of 50 centers and the U.S. gets half of them, that means only 25 locations in the entire country where participants will have to go to sign up and for periodic follow-up visits.

Names Project founder Cleve Jones thinks that means people in places like rural Sonoma County, where he now lives, will be left out. "It's going to be a situation where only those who've really learned to work the system will get this drug," he worries, and travel to San Francisco—likely to be the nearest site—will be "a big problem" for several friends in desperate need.

Jones, who has seen two friends do well in a 1592 trial and knows several others who urgently need the drug, thinks it is time for the community to mobilize. "There are people in the treatment activist community who think that Glaxo Wellcome is deliberately delaying development to maximize profits on AZT and 3TC," whose sales might decline if 1592 became available on a large scale, he notes. "I have not yet reached that conclusion, but it's getting harder and harder to forgive the delays. I've been an AIDS activist for 16 years and this is one of the most frustrating situations I've ever encountered," he declares. "The drug works and they know it. It's just stalling."

That sentiment seems just about unanimous among AIDS activists. ACT UP/Golden Gate has made 1592 an urgent priority and is developing a series of protest actions which it hopes to coordinate with other groups around the country. TAG is writing a new letter demanding a larger program which it will ask other groups to sign, and Smart hints that that is just the beginning. "I think Glaxo is going to come under strong attack from the community," he says. "Although the days of activism in the streets may appear to be over, there are a number of other ways the community may be able to hurt Glaxo Wellcome." ▼

AIDS ACTION NOW!
517 College Street, Suite 420, Toronto, Ontario, M6G 4A2
Tel: 416-928-2226 Fax: 416-928-2185

7 May 1997

Glaxo Wellcome Inc.
7333 Mississauga Road North
Mississauga, Ontario
Canada
L5N 6L4
Fax: 905-819-3396
Attention: David Krakovsky
Clinical Research

Dear Ladies and Gentlemen:

Re: Compassionate Access to 1592U89

We are writing to express our concerns about the compassionate use program for 1592 as described by you in our meeting of May 1, 1997.

The Numbers

First of all, we are shocked by the paltry 2000 spots in the adult program for Europe, Australia, Canada and the United States. As you will know, the number of AIDS cases in these countries is well over 700,000. Glaxo Wellcome has been a model of generosity with the 3TC open label program which was relatively unrestricted and, in total, provided 3TC to approximately 30,000 individuals. Why is there such a difference in these programs?

You indicated that your reasons for limiting the compassionate access are as follows:

1) supply problems as a result of the change in formulation.

This is obviously something that is difficult for the community to judge and is a common reason put forward to limit compassionate access. To alleviate the community's suspicions that this is not a valid reason, and in keeping with your stated intention to have a "transparent" relationship with the community, would you allow an independent production analyst to inspect your production capacities? Merck agreed to such an independent review and this was beneficial to both the company and the community which were at loggerheads over a similar supply issue.

We appreciate that drug supply may be a rate-limiting factor in the development of the compassionate use/open label program, however we would ask you to undertake to scale up production to meet the need.

AIDS Action Now!
7 May 1997

2) you must ensure adequate supply for the conduct of clinical trials.

We understand that you have approximately 33 trials either ongoing or in development. Would it be possible to prioritize the trials required for regulatory approval and then review the relative urgency of the conduct of some of the planned additional or supportive trials vis-à-vis the needs of the compassionate use program, in consultation with the community? This might allow you to better "balance a limited supply of drug with the competing needs of an extensive clinical development program and the compassionate use/open label study" keeping in mind that "[t]he ultimate goal is to meet the needs of individuals.... (your letter to the Canadian HIV/AIDS Community dated April 29, 1997)

3) there are more treatment options now than when 3TC entered into Phase III trials in June of 1993 and, therefore, you do not perceive that there is as much of a need; that there is not as much of a "drought" now as there was when you began the 3TC open label program in December 1993.

We find this argument hard to follow for two reasons: if you do not think that there is a real need for 1592 at this time, why have you imposed more limiting entry criteria than with 3TC and why have you capped the numbers of spots available? Secondly, we would suggest that for the individuals who have either exhausted all available options, or for whom their only option right now is to add one drug to a failing regimen, there is a real drought.

4) you have safety concerns about 1592; approximately 250 trial participants have taken 1592, and none for more than six months.

We are not advocating that everyone should abandon therapies which are working for a product which is just now beginning Phase III trials; however, a practice has evolved over the course of this epidemic to allow for compassionate access to a drug once Phase I and II trials are complete and the gross toxicities and adverse events are known. At this point, the acute safety concerns have been met and we acknowledge that there will, of course, be chronic safety concerns. However, this will be a staggered process of risk assessment - by the time that those who receive 1592 on a compassionate basis have been on the drug for six months, those trial participants will have had a further six months of exposure, and so on.

The Entry Criteria

We recognize that it is probably impossible to design a *limited* compassionate access program which will please everyone. Certainly, we feel that the entry criteria may need to be further "tiered" according to severity of the situation in order to most fairly ration the supply on the basis of need. This will probably depend, in part, on the size of the initial demand and would probably be best determined separately by each of Australia, Europe, Canada and the United States. Also, as supply increases we would expect to see the criteria made more liberal.

However, we do feel that your "salvage" program must be amended to adequately provide for mild to moderate AIDS Dementia Complex (ADC). Although we understand that you do have a clinical

trial for mild to moderate ADC, there are only 90 spots worldwide, and we do not consider it ethical to force people into a placebo-controlled clinical trial as their only hope of obtaining the drug. We recommend that the entry criteria be amended to add a category for those with mild to moderate ADC who have failed on or are intolerant of AZT and d4T. Even if the supply cannot meet the demand, we would prefer to encourage these individuals to apply so that we can assess the need and allow for a tiered system of access based on severity of need, as supply increases over time.

The Registration Process

You have indicated that the adult program will take place at geographically dispersed centres. We are vehemently opposed to this suggestion. There are numerous potential problems with such a system whereby an investigator for an area would hand pick individuals from his/her practice. When Merck Frosst initiated a program such as this in Canada it created a great deal of ill feelings toward the company. A practice has evolved in Canada in the last few years of compassionate access programs to utilize a centralized application and registration centre run by an arm of the Canadian HIV Trials Network. This has worked, is respected by the community, and is seen as the only fair and equitable way to allocate the limited supply of the drug. This would also allow us to better assess the real demand for compassionate access to 1592. We would, therefore, recommend that Canada be allowed to develop its own registration process in consultation with the community and that you utilize the Canadian HIV Trials Network as the registration centre and also as the Canadian contract research organization (CRO).

We understand that you would prefer to limit the Canadian sites for distribution to two or three which will be involved in the Phase III studies of 1592 and will, therefore, have some experience of 1592. We believe it is possible to have more sites with HIV-experienced physicians involved in the distribution of 1592 as was possible with 3TC. It is preferable that patients are able to stay with their own physicians and clinics for the continuity of their care, and that more physicians develop some experience of 1592. Clear guidelines in the protocol should ensure that the drug is appropriately used and monitored. At the very least, we will need more sites for distribution to reflect the geographical reality of AIDS incidence in Canada.

Possible Inter-Company Collaborative Compassionate Use Salvage Program

We are all aware that it will not be the best use of 1592 to take it as monotherapy, or to add it to a failing regimen; however, individuals who have exhausted all other options will have no choice. We are pleased that there are no restrictions on using 1592 with other experimental therapies; however, this does not ensure or facilitate that someone in need will be able to access other experimental therapies at the same time. For this reason, we query whether you would look at the possibility of an inter-company collaborative compassionate use salvage program, with companies such as Dupont Merck and Gilead, for individuals who have exhausted *all* options, so that such individuals could be offered two or three experimental therapies at once and a real hope of sustained benefit. Perhaps such a pilot program could be coordinated by a branch of the ICC.

AIDS Action Now!
7 May 1997

Future Consultations

We would appreciate seeing your draft protocol including the informed consent form so that we may provide you with some input. We would also be interested in seeing the Case Report Forms. We trust that you will continue to consult with us in a meaningful way through the development of this program.

Benefits of Compassionate Access

Lastly, we would ask you to consider the following possible advantages of a liberal compassionate access program:

- avoids negative publicity
- creates goodwill
- marketing - physician experience
  - word of mouth
- creates a market which will pressure third-party payers such as government drug plans and insurance companies - In Canada the widespread compassionate access to 3TC resulted in a great deal of pressure on the government drug plans to cover the drug for those on social assistance.
- creates an ultimate market - keeping someone alive until the drug is licensed.

The consequences of an inadequate program are obvious:

- some individuals irreversible or untreatable and, possibly preventable, opportunistic infections;
- some may die unnecessarily before access to 1592 is expanded.

It seems ironic that we are faced now with responding to such a limited compassionate use program, of less than 100 cases for Canada, while on May 15, 1997 Glaxo Wellcome representatives will be attending the Prix Galien ceremonies in Montreal nominated for their innovative new product, 3TC, and that in the media package for the launch of 3TC, GW prides itself on the fact that "[t]hrough the open-label program doses to 2800 people living with HIV/AIDS were able to access 3TC in Canada prior to its approval".

We look forward to your early response.

Yours very truly,

Maggie Atkinson
Co-Chair

GlaxoWellcome

CLINICAL RESEARCH DEPARTMENT

May 22, 1997

Maggie Atkinson
CTAC Advisory Team
AIDS Action Now! Co-Chair
517 College Street, Suite 420
Toronto, Ontario,
M6G 4A2

Dear Maggie:

Thank you very much for sending us your comments about the 1592U89 compassionate access programme discussed at our May 1st meeting. We have given much thought to your concerns and have discussed these issues with our international colleagues in the US and UK.

Comparing the 3TC programme to the proposed 1592U89 programme at this point in time is difficult. At the comparable point in 3TC's clinical development, the compassionate use programme that we are proposing for 1592U89 did not exist. In fact, the 3TC programme commenced after the majority of the patients had been enrolled into the pivotal phase III studies, and the efficacy/safety profile was better established.

We are initiating the 1592U89 compassionate use programme earlier, as we prepare to start enrollment into the phase III clinical studies. This is an "interim" programme designed to provide some drug to those people who need it, while still obtaining important information in this anti-retroviral experienced population, prior to initiating an expanded access programme. The numbers for this programme (2,500) are greater than those planned for the clinical trial programme during the same period. Towards the end of the year, as more supplies and data become available, we can then initiate the larger expanded access programme. The size of that program will be decided based on safety and efficacy data when it is available from the pivotal clinical studies.

In order to address your concerns we have taken each into consideration as follows:

1) Supply:

The following is a detailed review of the development of 1592U89, which we hope will address your concerns over the supply issues as a result of the change in formulation.

In the summer of 1995 following the merger of the two companies Glaxo Wellcome had a number of compounds in development for the treatment of HIV including: 3TC, 1592U89, 141W94, 1263W94, 935 and tucaresol. Resource was distributed amongst the projects according to the potential of each compound as demonstrated in the early stages of development - those compounds that showed the greatest potential had the greatest resource allocated. Limited resource was applied to 1592U89, which, with poor laboratory data appeared the least promising of the HIV drugs in development at that time. However, by November 1995, the situation had changed dramatically when 1592U89 demonstrated marked efficacy in the clinic. These contradictory results were unexpected. It is very unusual for a compound to perform poorly in the laboratory and then go on to show significant

Glaxo Wellcome Inc.
7333 Mississauga Road North
Mississauga, Ontario
Canada L5N 6L4
Telephone
(905) 819-3000
Fax
(905) 819-3098

promise in the clinic, as was the case with 1592U89. Manufacturing scale-up plans, usually initiated on the basis of promising laboratory results were, therefore not in place when these first results with 1592U89 emerged. Chemical resource had been fully assigned to other more promising compounds anticipating that they would be the preferred compound for further development. Fewer chemists worked on 1592U89 and consequently a robust manufacturing process had not been established.

Glaxo Wellcome has a history of working together with communities affected by HIV and was aware of, and very sensitive to the needs of people with HIV and the compassionate requirements for drug outside of the clinical development programme. Consequently, full human and financial resource was put behind the 1592U89 development programme and in particular the number of manufacturing staff was increased by over 300%. Although the manufacturing process was not robust, the chemists persevered and eventually scaled it up to produce greater quantities of 1592U89. It was clear, however, that this process would not support the anticipated large drug substance requirements of the clinical programme. It also became obvious that supply of drug could not be met from the pilot plant facilities (pilot plant is the intermediate step between the laboratory and full-scale manufacturing). Therefore as well as having to identify a new process, our chemists would have to transfer it rapidly into full scale manufacturing facilities. In addition to these challenges, it was also necessary to move the manufacturing project to the UK.

By the end of November a seemingly viable process was identified; one batch was made in the pilot plant during January 1996 and within 2 months the process was transferred to full production.

By March 1996 the new process was being operated at full scale production, eventually producing large quantities of 1592U89 powder ready for the next stage in manufacture. Due to the need to move 1592U89 through clinical development at a rapid pace and the future need for access on a compassionate basis for those people with no other treatment options, considerable risks were taken in transferring the process to production. Normally before transfer occurs several pilot plant campaigns would be carried out providing experience of often up to 20 batches at each stage of the process. On this occasion only a single pilot plant campaign was carried out producing only ONE batch at each stage. Glaxo Wellcome's manufacturing staff were requested to prepare for full scale production prior to the feasibility of the chemistry being established in the pilot plant. Scale-up from laboratory to full production can often take as long as 2 years or more, but with 1592U89 this was achieved in less than 6 months. All the effort, expertise and risk taking seemed to be paying off.

Everything was going well in primary manufacture until the first batch of 1592U89 was produced in June 1996. A problem was encountered, not with the actual chemistry, but with the physical form of the drug substance itself. The compound was proving difficult to filter and dry, furthermore the pharmacy department were experiencing difficulty in formulating it into capsules. Instead of the substance presenting as a fine powder ready to encapsulate, it was presenting as a large, very hard, solid mass. By this time 1592U89 was at late Phase II clinical development and although significant effort was made to try and resolve the problem, it soon became clear that the salt part of the molecule needed to be changed. This would have been a large undertaking at the very early stage of primary manufacture, but with a considerable amount of unusable drug substance already manufactured, it was a very serious problem, threatening the whole clinical programme. In the past, pharmaceutical drug development programmes have sometimes been discontinued with problems such as these, due to the potential long delays in clinical development programme. Once again resource was stepped up and the problem was resolved. This problem may have been identified earlier had more time been taken for pilot plant testing, highlighting the risks that are involved in fast-track development. After extensive tests on several different salt forms a suitable alternative salt was identified.

Within four months a new alternative salt had been identified, scaled up into the pilot plant and transferred into full scale production to produce the new version of 1592U89.

At the end of December 1996 and during early 1997 the new 1592U89 had to undergo strict bioequivalence tests enforced by regulatory authorities, as well as further toxicology studies. By the end of March 1997 the new version 1592U89 had passed all these tests and further primary scale-up is now planned. As a comparison, the quantity of 1592U89 planned at this stage of development is 10 to 20 times greater than that produced for other drugs.

1592U89 Development
Calendar of Events

January	
February	
March	New process for 1592U89 scale-up in operation.
April	
May	1592U89 in full scale manufacture.
June	Problem with salt identified.
July	
August	
September	
October	New salt identified and in full scale production.
November	
December	1592U89 undergoes regulatory tests.
January	
February	
March	1592U89 passes regulatory tests.
April	Full scale production.
May	Full scale production.
June	Full scale production.
July	Full scale production.

2) Prioritizing clinical trials:

At this point in the development of 1592U89, we are obligated to learn as much as we can about the utility of this drug in well-controlled clinical trials. We are attempting to balance this work with an early compassionate use programme to provide 1592U89 to those patients with immediate medical need for the drug. Indeed, in this effort we are already prioritizing clinical trials in order to accomplish both of these objectives.

3) Need:

Many treatment options exist now and we cannot encourage patients to forego currently marketed drugs with proven efficacy in favor of a new treatment about which very little is known at this

time. Who best will benefit from 1592U89 remains to be determined from the Phase III clinical trial programme.

4) Safety concerns:

We acknowledge that safety issues are an ongoing concern and may have less impact on people with very few options. This is why we are committed to compassionate access for 1592U89 and why the programme is starting so early in the clinical development programme.

5) Entry criteria:

At this early stage in development, the treating physicians need to determine who best qualifies for the drug based on their clinical judgment. We are open to applying a system designed in conjunction with physicians, yourselves and the Canadian HIV Trials Network (CTN). Your input into any additional criteria for selection will be considered.

6) Mild to moderate dementia patients:

Since no data is available to prove that 1592U89 is effective against dementia, the ongoing clinical trial (CNAB3001) needs to be completed as soon as possible to address this point. Patients in this trial are adding either 1592U89 or placebo to their existing treatment regimen, and are not subject to receive a substandard of care. We understand your concerns and as such we have agreed to broaden the entry criteria to include people with MSK stage 2 disease once recruitment into the clinical trial is complete. We believe the company would be considered irresponsible by allowing treating physicians to release an unproven drug at an earlier stage of the disease than this, as quite often early stage dementia can be confused with other conditions.

7) Registration Process:

As discussed at our meeting on May 1, we agree that there is a need to provide access to the drug across the country in the most equitable manner possible, and that the CTN could play a role in the registration and selection of applicants. After our meeting we held discussions with the CTN, and they have agreed in principle to assist us with the programme. The CTN will issue information to all physicians about the program, accept applications, and review and approve applicants for entry into the programme, very similar to their involvement with the saquinavir compassionate use programme.

The logistics of CTN's role need to be worked out once more information about the programme is available. Access will be based on geographic need as determined by the prevalence of HIV/AIDS in each region across the country. The above will ensure that participating centres will not be able to hand pick individuals from their own practice, and that all who apply will have an opportunity to access the drug. The overall programme will be conducted by a contract research organization (CRO).

Due to Canada's size, we did not want to limit Canadian centres to only two or three, and put forward a proposal for eight centres across the country, as discussed at our meeting on May 1. As a result of this week's compassionate use teleconference, we are able to implement this programme at approximately 12 centres across the country. The number of participants for each country should be finalized within the next week, and we will communicate this information to you as soon

as it is available. Individuals outside of these centres can apply for the programme through their physician. If they are approved, individuals will have to go to a participating centre for access to drug, and attend all study-related visits for assessment and data collection. Required visits will likely be every two months, and individuals can continue to see their own physician during this time. As we are collecting important safety and efficacy data, which will help shape the expanded access programme, consistency must be maintained by involving a limited number of centres/physicians world-wide.

8) Intercontinent collaborative programme:

A 1592U89 collaborative studies review team has been organized to review all external study proposals for scientific and clinical merit and strategic importance. This team has reviewed over 40 proposals to date, and a number of them have been accepted. Glaxo Wellcome is working with a number of collaborative groups including the ICC, ACTG, etc., to establish and conduct collaborative studies with 1592U89, as well as our other products. We remain open to collaboration. We hope that our colleagues in the industry will also feel the need to furnish drugs to those most in need at the earliest possible time in their development.

9) Future considerations:

We truly believe that opening this "interim" programme ahead of the expanded access programme is a way to provide early access to 1592U89. This will allow more information to be obtained, in order to use the drug in the best way possible for the expanded access programme, while trying to meet the varying needs of communities internationally.

We hope that this information helps to explain the rationale behind the programme more clearly. If in the future you would like to discuss any subject with us, we would be more than happy to meet with you.

Sincerely,

David Krakowsky, B.Sc. Phm., Pharm. D.
Clinical Research Manager,
Infectious Diseases

cc: T. McAuley
L. Binder
R. Guerin
C. Lafleur
R. Kort
C. McClure

1592 ACCESS COALITION

To: Sandy Thurman	From : Linda Grinberg	
Company: White House-AIDS Office	Telephone: 310-471-6565	
Fax Number: 1-202-632-1096	Fax Number: 310-471-4565	
Subject : GW Demand Letter, etc.	Date: 6/25/97	Pages: 16

Sandy:

Pursuant to our telephone conference today, I am refaxing the demand letter which was faxed to Glaxo last Tuesday a.m. Also included is the cover fax which went out to community ASO's, seeking endorsements, which was not included in the fax to Glaxo.

I am also faxing you copies of the correspondence between Maggie Atkinson of AIDS Action Now! in Toronto and GW which I think may also be of interest to you. As you will see, the GW reps she's been corresponding with have been quite a bit more communicative and forthcoming with her regarding production and supply issues.

Lastly, I am including an updated roster of members of the coalition.

Meanwhile, good luck in setting up that conference call and getting a written response this week. We anxiously will await word on both of these items.

Thank you, once again, for your ongoing efforts.

Linda

1592 ACCESS COALITION

VIA FACSIMILE

June 13, 1997

Mr. Robert Ingram
Chief Executive Officer
Glaxo Wellcome, Inc.
5 Moore Drive
Research Triangle, NC 27709

Re: Development of Abacavir (1592)

Dear Mr. Ingram:

Community treatment advocacy groups and activists watch with growing concern as the major pharmaceutical companies continue to reduce the size of compassionate use and expanded access programs for promising new AIDS drugs. The limited 1592 compassionate use program proposed by Glaxo Wellcome provides the most recent example of the industry's misguided policy on early access.

The individuals and organizations listed below call on Glaxo Wellcome to take the following actions regarding 1592:

I. **Compassionate Use Program**
   A. Commit to significantly increase the size of the compassionate use program scheduled to begin in July 1997. (It is anticipated that more than 10,000 patients worldwide may need 1592);
   B. Triage patients to ensure those in most critical need are given highest priority;
   C. Provide monthly progress reports to designated community representative(s) regarding production capacity and patient enrollment;
   D. Describe procedures to ensure equity of access and avoidance of preferential treatment to patients at selected sites;
   E. Provide the drug to patients who cannot access the medical sites designated by Glaxo. (Traditionally, compassionate use programs reach patients through their healthcare providers.)

II. **Expanded Access Program**
   A. Initiate an expanded access program at the earliest possible date in 1997;
   B. Provide details regarding inclusion/exclusion criteria, size and scope of program, distribution plans, and other pertinent information as soon as possible.

III. **Protocols and Clinical Trial Sites** - Provide information on 1592 protocols and identify clinical study sites, as promised, immediately.

IV. **Accelerated Approval**
   A. File for accelerated approval of 1592 no later than March 1998;
   B. Initiate rolling data submissions to FDA as soon as possible.

Promising new therapies such as 1592 must become available as soon as possible to people without treatment options who face disease progression or death. Community advocates and activists call upon Glaxo Wellcome and all AIDS drug manufacturers to recognize that people with advanced disease have a basic right to speedy access to new experimental therapies

when all other treatment options have failed.

We look forward to receiving your response to our concerns regarding 1592.

Sincerely,

1592 ACCESS COALITION

Ron Baker	David Gilden	Andrew Lipschitz, M.D.
Bill Bahlman	Linda Grinberg	Joel Martinez
Peter Cashman	John Iverson	Eileen Mitzman
Sally Cooper	Cleve Jones	Leigh Paidolfino-Danas
Paul Davis	Kate Krauss	Lili Rundback
Martin Delaney	James Learned	Matthew Sharp
Jeff Getty	Jules Levin	Theo Smart

Endorsements of AIDS Organizations:

ACT UP East Bay, Oakland, CA
ACT UP Golden Gate, San Francisco, CA
ACT UP Los Angeles, Los Angeles, CA
ACT UP New York, New York, N.Y.
AIDS Action Now, Toronto, CANADA
AIDS Project Los Angeles, Los Angeles, CA
AIDS Service Center, Pasadena, CA
Center for AIDS: Hope & Remembrance Project, Houston, TX
Community Prescription Service, New York, N.Y.
Community Research Initiative on AIDS (CRIA), New York, N.Y.
F.A.I.R./Foundation for AIDS and Immune Research, Los Angeles, CA
Gay Men's Health Crisis, New York, N.Y.
Healing Alternatives Foundation, San Francisco, CA
Log Cabin Republicans, Washington, D.C.
Mother's Voices, New York, N.Y.
N.A.T.A.P./National AIDS Treatment Advocacy Project, New York, N.Y.
POZ Publishing, Inc., New York, N.Y.
Project Inform, San Francisco, CA
PWA Health Group, New York, N.Y.
The River Fund, FL
San Francisco AIDS Foundation, San Francisco, CA
Treatment Action Group, New York, N.Y.
United Foundation for AIDS, Miami, FL
W.O.R.L.D., Oakland, CA

AGREED and ACCEPTED this ___ day of June, 1997:

By:_____ **Of:**_____
(Signature) **(Organization)**

Print Name:_____ **Phone:**_____ **Fax:**_____

cc: Jennifer McMillan
Steve LeFon

1592 ACCESS COALITION

To: Sandy Thurmond	From : Linda Grinberg	
Company: The White House, AIDS Czar	Telephone: 310-471-6565	
Fax Number: 1-202-632-1096	Fax Number: 310-471-4565	
Subject : Abacavir/1592	Date: 6/16/97	Pages: 4

Glaxo Wellcome has announced that it will shortly launch a compassionate use program for its new drug, commonly known as "1592". Activists throughout the nation who have worked with the company to develop this program feel it is inadequate to meet the need. The program offered thus far is severely limited in both size and compassion and will initially reach 2500 people worldwide. Plans for a larger expanded access program, also promised by Glaxo, have been delayed until the beginning of 1998, at the earliest.

By any standard, this is not good enough. The number of people with an immediate need for this drug continues to grow each week.

We need your support -- and that of your organization -- to improve upon this program.

While many people have shown clinical improvement with protease inhibitors, increasing numbers have now failed on all available combinations. Others have never been in a position to benefit because they lacked the other "new" unused companion drugs needed to make an effective combination therapy. People have simply run out of drug options. 1592 is the only new drug likely to become available in the near future to help those in the most desperate need. In preliminary testing, 1592 appears to be reasonably safe and highly potent -- perhaps 10 times more potent than AZT. It will make a critically needed addition to the arsenal of drugs needed to combat HIV.

We are asking you to join and support our efforts by adding the endorsement of your organization to the growing list of groups who have already signed on. We also ask that you circulate this fax and letter to other organizations as soon as possible. Every name adds to its strength.

If you have any questions or need more information about 1592 or the proposed program and why treatment activists find it inadequate, please contact Ron Baker at 415-543-4440. If you want to get more involved, please contact Jeff Getty at 510-653-6099. Please fax back your signed endorsements to 310-471-4666.

Time is of the essence. Thanking you in advance for your ongoing support and your prompt attention to this matter.

GlaxoWellcome

June 18, 1997

Maggie Atkinson
AIDS Action Now! Co-chair
102 Westminster Avenue,
Toronto, Ontario,
M6R 1N4

Fax 416-533-2127

Dear Maggie:

First of all, please be assured that Glaxo Wellcome certainly is committed to identifying what the best use of 1592 will be. We reiterate that we are committed to a considerably larger expanded access program in 1998.

We cannot, however, communicate the final numbers for the expanded program at this stage. We must be very careful to balance supplies with the clinical programs running throughout the world and ensure that important regulatory requirements are met. Because the expanded access program will be international in scope, it is also very important to be certain all the necessary resources are available in each country participating. I am sure that you would agree that it is important that patients in every country have access to the program and adequate drug supply, as quickly as possible once it gets started.

While we cannot change the drug supply for 1997, we have started communications with government bodies (USA and France) to discuss our manufacturing capacity. The French Minister of Health will be meeting our international manufacturing team on June 25th. We would be happy to place you in contact with the appropriate people for an independent assessment of these discussions.

We recognize the contribution of the HIV/AIDS community and the important role that it has played in bringing treatment of this disease as far as it has come in the last 15 years. We ask now of AIDS Action Now!, that you stay focused and keep communication lines open. Our common objective is truly the rapid approval of this new treatment so that it can be made available to all who can benefit.

Glaxo Wellcome Inc.

Bureau d'affaires du Québec
771, rue Gougeon
Saint-Laurent (Québec) H4T 2B4

Administration
(514) 738-8898
1 800 463-6214

Télécopieur
(514) 738-9391

Centre de renseignements pour le [illegible] 268-0324 Information médicale : 1 800 668-6063 Gestion des commandes : 1 800 387-7374

Glaxo Wellcome is, as it always has been, open to community consultation. We are committed to meeting with you as often as necessary during the next months to address issues that could arise (such as assistance with travel costs for patients in outlying regions). As always we hope to maintain a collaborative relationship with you, our customer, and we ask that patience prevail and that our past record of compassion and leadership in community consultation be taken into consideration.

Glaxo Wellcome Inc. (Canada) considers the relationship they have with you an important one. This is why they have extended an invitation to you to attend a very important occasion marking the culmination of ten years of commitment and effort from many of our employees, and the start of a world mandate in pharmaceutical manufacturing. This invitation stands should you choose to participate as a colleague, and not as a demonstrator.

Maggie, we have worked very hard, to be able to respond in writing to some of your concerns and recognize that we are unable to provide you with all the details you wish at this time. I hope that you will understand that we must coordinate such communications globally and manage expectations about 1592 very carefully. I want to continue to work with you on this issue and look forward to discussing the Canadian 1997 Open label (compassionate use) program and plans next week with our CTAC liaison group.

I can be reached through my voice-mail 1-800-463-6314 ext. 347 or at the Delta Meadowvale (905)821-1981 this evening. Please let me know you of your decision, whether you will accept the invitation to the facility opening or not.

Sincerely,

Patricia

Patricia Rowe
Manager, HIV/AIDS Relations

cc Anita Kidgell - Manager, Product Communications, Group Public Affairs