ONE HUNDRED EIGHTH CONGRESS

Congress of the United States

House of Representatives

COMMITTEE ON GOVERNMENT REFORM

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June 30, 2004

Jean-Pierre Garnier, Ph.D.
Chief Executive Officer
GlaxoSmithKline
c/o Washington Office
1500 K Street, NW, Suite 650
Washington, DC 20005

Dear Dr. Garnier:

I am writing to urge that you reconsider GlaxoSmithKline's decision to withdraw from a major clinical trial involving HIV treatment in African and other developing countries. Your company's action is undermining efforts to determine how to treat millions of people infected with HIV around the world.

The study, which is sponsored by the National Institutes of Health (NIH), is designed to compare three treatment regimens among more than one thousand patients in eight developing countries. It is the first major study to assess how best to treat HIV infection in areas of the world hardest hit by the AIDS epidemic.

Drugs manufactured by five companies are essential for the planned research. In accordance with longstanding practice, four of these companies — Boehringer-Ingelheim Pharmaceuticals, Bristol-Meyers Squibb, Gilead, and Merck — have agreed to donate their drugs free of charge.

Like the other companies, GlaxoSmithKline promised to participate in this ground-breaking investigation. Unfortunately, your company reversed its position and withdrew from the study last year. Efforts by the investigators to restore GlaxoSmithKline's participation have now also been rebuffed. As a result, the treatment of patients in the study, which was scheduled to begin in the first quarter of 2004, has been delayed indefinitely.

My staff has contacted the investigators in charge of the study. We have learned that GlaxoSmithKline withdrew from the study after the investigators proposed a revised research protocol that would compare the effectiveness of drug combinations containing Combivir, a leading GlaxoSmithKline product, with the effectiveness of drug combinations without

Combivir. According to a senior investigator involved with the study, your company attempted to pressure researchers to drop this comparison "as a quid pro quo for providing the drug."

On scientific and ethical grounds, the investigators decided against changing the protocol as requested by GlaxoSmithKline. E-mail communications indicate that GlaxoSmithKline then refused to provide any "form of GSK support" for the study on the grounds that it is "currently not a priority for GSK." GlaxoSmithKline took this position even though NIH research has provided much of the basis for the company's lucrative sales of several widely used HIV drugs, including the very drug that the company is declining to donate for this study.

I urge you to rethink your company's position. The investigators running the study are world-class scientists. GlaxoSmithKline should be supporting — not undermining — this essential HIV research in Africa and other areas of the developing world.

Background

From the beginning of the HIV epidemic, government-sponsored studies have played a vital role in providing evidence to guide treatment. From the first studies of zidovudine (AZT) to research on today's multi-drug antiretroviral regimens, NIH has been the world leader in clinical HIV research.

In recent years, AIDS scientists have become concerned about the relative lack of data comparing different multi-drug regimens in the developing world, where the vast majority of HIV infections occur.[1] Because the genetic makeup of HIV, resistance patterns, and coexisting infections with other organisms may differ in developing countries, attention began to focus on this gap in scientific knowledge.

Five years ago, the NIH-funded Adult AIDS Clinical Trials Group, the largest HIV/AIDS clinical trial organization in the world, initiated plans to conduct a major HIV/AIDS clinical trial in resource-constrained settings overseas.[2] These plans developed into Protocol A5175, which is an NIH-sponsored, peer-reviewed clinical trial involving over a thousand patients at twelve sites

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[1] Adult AIDS Clinical Trials Group, *A5175, Phase III, Randomized, Open-Label Evaluation of the Efficacy of Three Nucleoside Reverse Transcriptase Inhibitor Combinations for Initial Antiretroviral Treatment of HIV-1 Infected Persons in Resource-Limited Countries, Draft Version 0.8*, 42 (Dec. 2, 2002) ("To date, it is not known which combination of antiretroviral agents provides the most benefit for HIV-infected persons in resource-limited countries").

[2] E-mail from Dr. Thomas Campbell and Dr. Robert Schooley to Minority Staff, Government Reform Committee (June 28, 2004).

in Brazil, Haiti, India, Malawi, Peru, South Africa, Thailand, and Zimbabwe.[3] The study was designed in coordination with investigators from the countries participating in the study.[4]

The initial study design for Protocol A5175, which was finalized in December 2002, would have compared three regimens of drugs:

A. Combivir[5] twice daily + Sustiva[6] once daily;
B. Combivir twice daily + Viread[7] once daily; and
C. Combivir twice daily + Videx[8] once daily.

Under some circumstances, Viramune[9] could be substituted for Sustiva in Arm A of the trial.

At the time, the Adult AIDS Clinical Trials Group asked the five companies that manufacture drugs essential for the research to donate them. This request was in keeping with the longstanding practice of pharmaceutical companies' providing drugs for NIH research.[10]

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[3]The 12 sites are as follows: Rio de Janeiro, Brazil; Porto Alegre, Brazil; Port-au-Prince, Haiti; Chennai, India; Pune, India; Blantyre, Malawi; Lilongwe, Malawi; Lima, Peru; Johannesburg, South Africa; Durban, South Africa; Chiang Mai, Thailand; and Harare, Zimbabwe.

[4]E-mail from Dr. Thomas Campbell and Dr. Robert Schooley, *supra* note 2.

[5]Combivir also is known by the generic names lamivudine and zidovudine.

[6]Sustiva also is known by the generic name efavirenz.

[7]Viread also is known by the generic name tenofovir.

[8]Videx also is known by the generic name didanosine.

[9]Viramune also is known by the generic name nevirapine.

[10]It is the general practice of the pharmaceutical industry to donate drugs to NIH-sponsored clinical trials. Up to this date, GlaxoSmithKline appeared to comply with the industry standard, donating drugs for use in federally sponsored studies. *See, e.g., AIDS Therapy: Company Issues Statement on Antiretroviral Treatment Study* (Jan. 9, 2004) ("GSK has collaborated on this ACTG study since 1997, supplying Combivir (and other medications) for the drug regimens and financial support"); NIH, *Combination, Order of Anti-HIV Drugs Makes a Difference in First Time Recipients* (Dec. 10, 2003) ("Pharmaceutical sponsors [GlaxoSmithKline, Bristol-Myers Squibb, Pfizer] contributed medications and financial support for the study"); *AIDS Clinical Trial Group Begins Clinical Study of Protease Inhibitor*, Doctor's Guide (Feb. 13, 1997) (online at http://docguide.com/dg.nsf/PrintPrint/0093C3374B987F7E8525643E0058F033) ("Glaxo Wellcome [GSK] has provided logistical support and has donated Retrovir and Epivir for use in the trial").

Researchers approached Boehringer-Ingelheim Pharmaceuticals (maker of Viramune), Bristol Meyers-Squib (maker of Sustiva and Videx), Gilead (maker of Viread), GlaxoSmithKline (maker of Combivir), and Merck (distributor of Sustiva in Africa). In February 2003, GlaxoSmithKline agreed to provide Combivir for the study.[11] The other companies also agreed to participate.

Soon after the agreement with GlaxoSmithKline was reached, however, new research results from the United States indicated that the planned Combivir/Videx regimen (Arm C) would likely prove inferior to the Combivir/Sustiva regimen (Arm A).[12] These results suggested that the original study design was no longer scientifically valid and would be unethical to pursue. To avoid giving some subjects a substandard treatment regimen, the investigators concluded the protocol had to be altered.[13]

By the late spring of 2003, the team of investigators decided to change the third regimen to one that potentially would be more useful in resource-limited settings. The revised protocol would compare:[14]

A. Combivir twice daily + Sustiva once daily;
B. Combivir twice daily + Viread once daily; and
C. Viread once daily + Emtriva[15] once daily + Sustiva once daily.

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[11]E-mail from Dr. Thomas Campbell and Dr. Robert Schooley, *supra* note 2. *See also* E-mail from Edde Loeliger, Director, Clinical Development & Medical Affairs, Europe, GlaxoSmithKline, to Dr. Robert Schooley, Director, Colorado Center for AIDS Research, *RE: ACTG5175 & HTPN052* (Apr. 17, 2003).

[12]Adult AIDS Clinical Trials Group, *Executive Summary, ACTG Protocol A5095, Phase III, Randomized, Double-Blind Comparison of Three Protease Inhibitor-Sparing Regimens for the Initial Treatment of HIV Infection* (Feb. 20, 2003).

[13]E-mail from Dr. Thomas Campbell and Dr. Robert Schooley, *supra* note 2.

[14]Adult AIDS Clinical Trials Group, *A Phase III, Randomized, Open-Label Evaluation of the Efficacy of Once-Daily Protease Inhibitor and Once-Daily Non-Nucleoside Reverse Transcriptase Inhibitor-Containing Therapy Combinations for Initial Treatment of HIV-1 Infected Subjects From Diverse Areas of the World, Draft Version 0.16*, 45-46 (Feb. 20, 2004).

[15]Emtriva is also known by the generic name emtricitabine.

GlaxoSmithKine's Actions

In May 2003, GlaxoSmithKline contacted investigators to object to the new third arm that no longer included its drug, Combivir. The company indicated that without additional changes, it would neither participate in the study nor donate Combivir.[16]

On scientific grounds, investigators opted against changing the protocol as requested by GlaxoSmithKline.[17] Dr. Robert Schooley, the International Studies Coordinator of the Adult AIDS Clinical Trials Group, told GlaxoSmithKline officials that he believed that it was neither in the interests of the patients nor the company to "attempt to force international investigators to use a regimen they did not feel was appropriate as a quid pro quo for providing GlaxoSmithKline drugs for the trial."[18]

Researchers also concluded that it was not feasible to avoid all use of Combivir in the study, given the drug's key role as part of the gold-standard regimen in treating HIV.[19] This left researchers in the difficult position of needing drugs manufactured by five companies, but only having access to drugs from four companies. While some additional modifications were later made to the protocol, your company's refusal to participate did not change.

In early 2004, the researchers sought GlaxoSmithKline's permission to purchase Combivir through the Accelerating Access Initiative.[20] This is a program that provides access to HIV/AIDS care and treatment for patients in developing countries at "not for profit" pricing.[21] By the investigative team's calculations, NIH could have purchased Combivir for the study for approximately $300,000 through the Accelerating Access Initiative.[22] According to investigators, this expense, while a break with precedent, would have allowed the study to proceed.

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[16]E-mail from Dr. Thomas Campbell and Dr. Robert Schooley, *supra* note 2.

[17]E-mail from Dr. Thomas Campbell and Dr. Robert Schooley, *supra* note 2.

[18]E-mail from Dr. Robert Schooley to Minority Staff, Government Reform Committee (June 21, 2004).

[19]*Id.*

[20]*Id.*

[21]As a member of the Accelerating Access Initiative, GlaxoSmithKline offers anti-retroviral AIDS medications to governments of the least developed countries and to not-for profit organizations at discounted, preferential prices. Under this Initiative, Combivir is available at a cost of 90 cents per patient per day. GlaxoSmithKline, *Access to Health Care, Preferential Pricing* (online at www.gsk.com/about/pricing.htm#HIV).

[22]E-mail from Dr. Thomas Campbell and Dr. Robert Schooley, *supra* note 2.

GlaxoSmithKline, however, refused this request. On May 6, 2004, Dr. John Sykes, Medical Director of GlaxoSmithKline, wrote to senior officials at NIH:

> The above study has been re-reviewed and discussed at some length within the organization as you are aware the original study design was initially supported by GSK as it had special interest for the resource-poor setting. The current protocol reviewed addresses a question that is currently not a priority for GSK. The extension of preferential or not-for-profit pricing of ARV's [antiretrovirals] for clinical trials constitutes a form of "GSK support" and therefore we would not be in a position to supply. [23]

The company declined to provide its drug to investigators at anything less than U.S. retail prices. Investigators calculated that this move would represent a 2,000% markup, costing an estimated $6 million.[24]

Implications for the Study

GlaxoSmithKline's actions have led to an indefinite delay in efforts to understand the best way to treat HIV in the developing world. Investigators had been ready to begin treating patients under Protocol A5175 in the first quarter of 2004.[25] However, without supplies of Combivir, and with NIH understandably reluctant to divert $6 million from other research projects to purchase Combivir at U.S. retail prices, the study has come to a standstill.

This delay has major consequences. As each month goes by, clinicians will lack access to the best possible data on treating HIV in developing countries. The human costs of the delay will literally be measured in lives.

The delay is also wasting U.S. taxpayer dollars. Launching a major international clinical trial requires a substantial investment before the first patient is treated. Investigators began training personnel in July 2002 and gradually built up the physical and human resources capacity to conduct a large-scale study. For several months, however, this investment has been idle.

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[23]E-mail from John Sykes, Medical Director, MENA/SSA, to Debra Payne, NIH/NAID (May 6, 2004).

[24]E-mail from Dr. Thomas Campbell and Dr. Robert Schooley, *supra* note 2.

[25]*Id.*

Researchers estimate that ongoing expenses, including salaries and maintenance of physical equipment, exceed $2 million per year.[26]

The result is a disturbing precedent. The investigators who designed Protocol A5175 are among the best AIDS researchers in the world. Their scientific decisions about how to design their own trials must be respected. If companies come to view participating in NIH research as an option to be decided on narrow commercial grounds, then NIH-sponsored clinical research for a range of life-threatening diseases could be seriously impaired.

GlaxoSmithKline's Corporate Responsibility

GlaxoSmithKline has a distinguished record of drug development for HIV and has rightly portrayed itself as a leader in fighting the AIDS epidemic. You have stated, "GSK remains committed to addressing the challenges of HIV and we take our responsibilities . . . very seriously."[27] GlaxoSmithKline also supports an array of charitable activities to fight the epidemic around the world.[28]

The company's current actions stand in stark contrast to these public commitments. I recognize that comparing drug combinations with Combivir against a drug combination that does not contain Combivir could be damaging to GlaxoSmithKline's bottom line if the non-Combivir combination proves more effective. But the objective of the study must be to find out what works — not to protect GlaxoSmithKline's profits. The fact that you may not like the outcome of the study is not a legitimate reason for withdrawing support.

GlaxoSmithKline's actions are even more objectionable given the major role that federally funded studies have played in the development and commercial success of Combivir. Combivir is a combination of two active drug ingredients, zidovudine (AZT) and lamivudine (3TC). Using an NIH-derived laboratory test, NIH researchers were the first to prove that AZT was effective against HIV in human cells.[29] Moreover, NIH has also sponsored major clinical trials that support the use of AZT, 3TC, and Combivir. [30]

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[26]Investigators had been ready to begin treating patients under Protocol A5175 in the first quarter of 2004.

[27]Jean-Pierre Garnier, *Message for World AIDS Day* (Dec. 1, 2002) (online at http://www.gsk.com/about/world_aids_day_2002.htm).

[28]GlaxoSmithKline, *Corporate Responsibility Report 2003* (2003).

[29]*Patent Quagmire: Who Invented AZT? Big Bucks Are Riding on What Sleuths Find*, Wall Street Journal (Oct. 21, 1993).

[30]S. Hammer et al., *A Controlled Trial of Two Nucleoside Analogues Plus Indinavir in Persons with Human Immunodeficiency Virus Infection and CD4 Cell Counts of 200 per Cubic*

GlaxoSmithKline earned more than $1 billion from sales of Combivir from 2001 to 2003 in the United States alone.[31] It would be appropriate for GlaxoSmithKline to acknowledge this heavy debt to NIH by participating voluntarily in Protocol A5175.

Conclusion

AIDS has plagued the world for over 20 years, decimating entire communities and threatening nations. It is long past time for a major trial to address how best to treat HIV in Africa and other developing nations.

I urge you to reconsider your company's withdrawal from Protocol A5175. This action is impairing scientific progress on HIV and setting a terrible precedent for future clinical research. A reversal in GlaxoSmithKline's position, by contrast, would represent a major step in public-private cooperation against the AIDS epidemic.

I request a reply to this letter by July 9, 2004.

Sincerely,

Henry A. Waxman
Ranking Minority Member

Millimeter or Less, New England Journal of Medicine, 725–733 (Sept. 11, 1997); D. Kuritzkes et al., *Lamivudine in Combination with Zidovudine, Stavudine, or Didanosine in Patients with HIV-1 Infection: A Randomized, Double-Blind, Placebo-Controlled Trial*, AIDS, 685–694 (Apr. 16, 1999); S. Hammer et al., *A Trial Comparing Nucleoside Monotherapy with Combination Therapy in HIV-Infected Adults with CD4 Counts from 200 to 500 per Cubic Millimeter*, New England Journal of Medicine, 1081–1090 (Oct. 10, 1996); M. Fischl et al., *The Safety and Efficacy of Zidovudine (AZT) in the Treatment of Subjects with Mildly Symptomatic Human Immunodeficiency Virus Type 1 (HIV) Infection*, Annals of Internal Medicine, 727–737 (May 15, 1990); P. Volberding et al., *Zidovudine in Asymptomatic Human Immunodeficiency Virus Infection: A Controlled Trial in Persons with Fewer than 500 CD4-Positive Cells per Cubic Millimeter*, New England Journal of Medicine, 941–949 (Apr. 5, 1990).

[31] *The Golden Age of Antiretroviral Drugs*, Forbes (Oct. 27, 2003).