SUMMARY MINUTES - 31st MEETING

Anti-Infective Drugs Advisory Committee

January 16, 1987

Division of Anti-Infective Drug Products
Office of Biologics Research and Review
Center for Drugs and Biologics
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Members Present

Itzhak Brook, M.D., Chairman
Alan S. Cross, M.D.
Margaret Hammerschlag, M.D.
Frederick L. Ruben, M.D.
Stephen E. Straus, M.D.
Walter T. Hughes, M.D.
Stanley M. Lemon, M.D.
Lewis W. Marshall, M.D.
Judy A. Bean, Ph.D.
Raoul L. Wientzen, M.D.
Calvin M. Kunin, M.D.

Absent

Nancy M. Newman, M.D.
Kirk R. Wilhelmus, M.D.

Executive Secretary

Thomas E. Nightingale, Ph.D.

FDA Participants and Observers

Edward Tabor, M.D.
Ellen Cooper, M.D.
Lawrence Hauptman, Ph.D.
James Bilstad, M.D.
Paul Parkman, M.D.
Robert O'Neil, Ph.D.
Joseph Price

Burroughs Wellcome Participants

Dr. David Barry
Dr. Dannie King
Dr. Sandra Nusinoff-Lehrman
Dr. Phil Furman
Dr. Ken Ayers
Dr. Bob Blum
Ms. Mary Maha
Dr. Fred Schmitt
Dr. Hugh Tilson

These summary minutes for the January 16, 1987 meeting of the Anti-Infective Drugs Advisory Committee were approved on 1/12/88.

"I certify that I attended the January 16, 1987 meeting of the Anti-Infective Drugs Advisory Committee and that these minutes accurately reflect what transpired."

T.E. Nightingale
Thomas E. Nightingale, Ph.D.
Executive Secretary

Itzhak Brook, M.D.
Chairman

INVITED GUESTS AND CONSULTANTS

Donna Mildvan, M.D.	Beth Israel Hospital - New York City
Robert R. Redfield, M.D.	Walter Reed Army Institute of Research
Paul Volberding, M.D.	San Francisco General Hospital
Martin S. Hirsch, M.D.	Massachusetts General Hospital
Margaret Fischl, M.D.	University of Miami
Michael Lange, M.D.	St. Luke's - Roosevelt Hospital Center
Douglas Richman, M.D.	V.A. Medical Center - San Diego
Cliff Lane, M.D.	Laboratory of Immunoregulation - NIAID
Samuel Broder, M.D.	Division of Cancer Treatment - NCI

1. The meeting convened at 8:50 a.m., January 16, 1987, in Conference Rooms G and H, Parklawn Office Building, with Dr. Itzhak Brook, the Committee Chair, presiding. The entire meeting was open to the public. The purpose of the meeting was to review the safety and efficacy of azidothymidine (AZT) in the treatment of human immunodeficiency virus (HIV) infected patients. There was no response to the Chair's invitation for participation in the open public hearing, although several persons did make comments later during the open committee discussion.

2. The Chair recognized Mr. Joseph Price of the Meeting Management Branch, Office of Scientific Advisors and Consultants, Center for Drugs and Biologics, Food and Drug Administration (FDA) who read a statement regarding potential conflicts of interest between the Burroughs Wellcome Company and FDA-sponsored participants at this meeting. The Agency had granted full waivers permitting total participation of those members and consultants serving under appointments as special government employees. Other invited guests had submitted a declaration of their association with the sponsor and product under discussion, and their participation at this meeting was considered to be in the public interest.

3. Dr. Edward Tabor, Director of the Division of Anti-Infective Drug Products, FDA, made introductory comments on the role of the advisory committee and consultants in the review of drugs for treatment or prevention of infectious diseases.

4. Dr. Ellen Cooper, reviewing medical officer for AZT and other drugs for the treatment of acquired immunodeficiency syndrome (AIDS) and other forms of HIV infection, addressed regulatory and scientific issues in the review of the New Drug Application (NDA) for AZT. The application under review today was submitted on December 2, 1986, for "the management of certain patients with serious manifestations of infections caused by HIV". Given the importance of pending FDA action on this drug, experts in the treatment of the disease, other public health representatives and the scientific community at large were invited to provide information relevant to approval and questions raised by the data. She noted that regulatory and policy requirements called for adequate and well-controlled clinical investigations, generally from at least two geographically separate centers to demonstrate confirmability of the clinical research. This NDA however, was based on one multicenter placebo-controlled study which was stopped prior to its planned completion date. Subsequent review of data accumulated since September 1986 when the study was switched to an open label continuation will be very important. A preliminary analysis of some of this supplementary data was submitted to the Agency on January 12 and had only been briefly examined. There were also no good data on the in vivo antiviral efficacy of the drug which would support its assumed mechanism of action based on its ability to inhibit HIV in vitro at low concentrations, despite the usual requirement for in vivo evidence of specific anti-infective activity. Another issue is the potential for widespread prescribing of

the drug to persons outside of the approved indications if general marketing approval is granted, with longer administration and use in less ill patients than are supported by the studies which could lead to approval. Since the drug has been administered to only two specific groups of patients in relatively advanced stages of disease, late AIDS-related complex (ARC) and AIDS following an initial episode of Pneumocystis carinii pneumonia (AIDS/post PCP) for a limited time (two and one half to six months) in the placebo-controlled study, it is not known how well or how poorly asymptomatic patients or those with minimal symptoms may fare after years of exposure, even if they tolerate it better over the short term. A further complication is the fact that the natural history of HIV infection and the progression from the earliest stages through AIDS is not well established, and if a significant proportion of patients are able to effectively inhibit the virus by their own immune response and avoid a progressive deterioration, administration of an antiviral agent may be of more harm than benefit since these drugs are relatively toxic. Only properly controlled, long-term studies will provide information on means of identifying those infected patients who are likely to progress to more serious disease and defining the optimal intervention point in the progress of infection. How best to identify and characterize the patient group who benefited from administration of the drug has not been clearly shown, since patient selection and stratification in the data to be reviewed were derived from late ARC and AIDS/post PCP patients with absolute T-helper cell counts of less than 500 per cu mm and cutaneous anergy, with stratification by T4 counts above or below 100. Committee advice was sought on how best to categorize patients for both safety and efficacy. Should it be based on entry T4 counts, on clinical classification of AIDS vs ARC, or a combination of both? Dr. Cooper informed members that there were unresolved scientific and regulatory issues including drug interactions, possible systematic bias in the clinical trial due to premature unblinding, incompletely documented causes of death, confusion over whether certain events were symptoms or adverse experiences, and the lack of preclinical animal studies which are normally required before a drug is considered for approval.

5. Dr. Dannie King of Burroughs Wellcome introduced their firm's speakers and topics.

a. Dr. Sandra Nusinoff-Lehrman presented the preclinical evaluation of AZT including in vitro findings and efficacy in animal models. A summary of data showed: AZT is a potent inhibitor of HIV as well as several other oncogenic and non-transforming mammalian retroviruses; animal models of retrovirus-induced disease indicate that AZT may modify the course of murine and feline leukemia virus infections; AZT is a potent inhibitor of a variety of gram-negative enterobacteriaceae; and except for its ability to inhibit Giardia lamblia, AZT is not active in vitro against a variety of other viruses, fungi, or parasites which may cause opportunistic infections in patients with AIDS.

b. Dr. Phil Furman reviewed the mechanism of action of AZT. Phosphorylation of AZT to the monophosphate occurs by cellular cytosolic thymidine kinase, with subsequent phosphorylation to di- and tri-phosphate forms catalyzed by cellular thymidine kinase and presumably, nonspecific kinases, respectively. High levels of AZT monophosphate were formed in both infected and noninfected cells, whereas levels of AZT di- and tri-phosphate were low. AZT triphosphate is a potent and selective competitive inhibitor of HIV reverse transcriptase, with cellular levels of AZT triphosphate being more than sufficient to inhibit this enzyme. Since AZT monophosphate is an alternative substrate inhibitor of cellular thymidylate kinase, inhibition of this enzyme causes a reduction of intracellular dTTP which is a competing substrate for HIV reverse transcriptase, therefore it is possible that AZT could self-potentiate the inhibition of reverse transcriptase. Finally, incorporation of AZT monophosphate into a primer template by HIV reverse transcriptase might result in chain termination which may be viricidal.

c. Dr. Ken Ayers summarized toxicologic studies completed to date. General toxicity studies including in vitro hemolysis tests, and acute or up to four week intravenous dosing of rats, mice and dogs showed no treatment-related alterations. Oral dosing of rats, dogs and cynomologus monkeys resulted in some toxicity, most notably of the hematopoietic system. Genetic testing included the AMES test which showed AZT was non-mutagenic, while the mouse lymphoma cell assay, cultured human lymphocytes, and BALB/C-3T3 assay all gave positive findings at high concentrations, although an in vivo cytogenetic trial in rats showed no chromosomal alterations in bone marrow. Limited reproductive trials in rats and rabbits have shown no embryotoxicity or fetotoxicity. The timetable for planned studies was briefly summarized.

d. Dr. Bob Blum presented pharmacokinetic and bioavailability data from Phase I trials in humans. Patients were given single or multiple IV or oral doses, with plasma and urine analysis of AZT levels, as well as the major metabolite, a glucuronide form of AZT (GAZT). The results showed AZT had a plasma half life of one hour, and a total body clearance of about 1900 ml/min/70 kg. Hepatic glucuronidation accounted for 1500 ml/min/70 kg of this with the remainder being renal clearance. Plasma protein binding was low, the volume of distribution was large, and from a CSF-to-plasma ratio of 0.5, it appeared that the drug crossed the blood-brain barrier.

e. Ms. Mary Maha reviewed the clinical results of the Phase I study. The 35 patients enrolled in the initial six week IV and oral dosing protocol included 23 with AIDS and 12 with ARC. Patients completing the initial course were eligible to continue on AZT therapy, and 20 were still receiving the drug, as of January 16, 1987. Chronic doses have been modified for each patient in response to presumptive toxicity or onset of opportunistic infections which required other chemotherapy. Current doses range from 200-2500 mg/day, with the highest

dose for the longest duration being 500 mg every 4 hours for 32 weeks without toxicity, with some patients on lesser doses for as long as 72 weeks. No patient developed hepatic, renal or cardiac toxicity, although there were signs of bone marrow suppression including anemia, leukopenia, neutropenia and occasional thrombocytopenia. Dose reductions or temporary cessation of therapy, along with transfusions usually resulted in correction of hematologic problems. Data were presented on the occurrence of opportunistic infections, deaths, and clinical responses. The most notable clinical responses were weight gains, resolution of HIV-associated symptoms such as fevers, malaise, low appetite, nausea, night sweats, improvement of HIV-associated neurologic signs, and spontaneous clearing of nailbed fungal infections and aphthous stomatitis. Increases in helper T cells were seen as well as development of positive responses to skin test antigens.

f. Dr. Dannie King presented results of the Phase II multicenter trial conducted at 12 institutions. A total of 282 patients were on the trial when it was ended, with 145 on drug and 137 on placebo. Inclusion criteria included post-Pneumocystis carinii pneumonia, a T4/T8 ratio below one, cutaneous anergy, neutrophil counts equal to or greater than 1000, absolute T4 counts of less than 500, and positive HIV antibody status. A variety of clinical and laboratory parameters were monitored with data reviewed by a committee which recommended that the placebo portion of the trial be stopped after the 16 week review, and all patients be started on AZT. At the 16 week interval, there were 19 deaths in patients on placebo and one in the AZT group, and as of 1/16/87 there were 32 and 8 deaths, respectively. When mortality was stratified by diagnosis (AIDS vs ARC) or T4 counts (high vs low), patients in all four subsets on AZT fared better than placebo, and when probability of survival or the probability of acquiring an opportunistic infection were calculated, these data also favored the AZT groups. Data on Karnofsky scores which represent the ability of a patient to perform normal daily functions, the sum of symptoms scores (malaise, fatigue, headache, nausea, etc.), change in body weight, changes in T4 cell counts, and cutaneous responsiveness to skin test antigens all showed general improvement in the AZT group, with patients having higher initial T4 counts showing better responses. He showed several slides to explain problems in data tabulation and analysis since patients entered the initial AZT or placebo groups over four and one half months, then the trial was altered and all patients in the placebo group began receiving AZT over a three to four week period. Since the study was continuing, data submitted to the Agency only included 127 of the original AZT group who received drug for roughly six months, and 86 of the original placebo group who have received AZT for 12 weeks or longer, although these numbers were increasing.

g. Dr. Sandra Nusinoff-Lehrman presented data from safety monitoring of the Phase II trial. A total of 221 out of the 282 patients reported at least one adverse clinical experience, with only nausea, myalgia and insomnia being statistically more frequent in the AZT group. Complaints of headaches were equal in the two groups, although AZT recipients were more likely to rate their headaches as moderate or severe. Bone marrow suppression including anemia, leukopenia and neutropenia were the primary hematologic toxicity responses. Dose adjustments and temporary discontinuations were more frequent in AZT patients, while permanent discontinuations due to death or other necessary medical needs were more common in the placebo group. Anemia was also managed by transfusion, with a larger proportion of AZT patients receiving either single or multiple transfusions, and patients with low T4 counts at entry were more likely to require transfusions. It was noted that patients unable to tolerate AZT tended to show this intolerance early in the treatment, and continued to require support. The only drug to show a toxic interaction with AZT was acetaminophen.

h. Dr. Sandra Nusinoff-Lehrman briefly reviewed clinical virology data. Monthly blood samples were assayed for HIV by reverse transcriptase detection in the supernatants of co-cultured cells. There was no indication of an antiviral effect in the patients studied. Some of the investigators had examined P24 antigen levels and found lower values during the early phase of treatment in AZT patients, although the relationship between these changes and HIV replication, pathophysiology and clinical disease were not known.

i. Dr. Fred Schmitt reviewed neuropsychiatric data. A preliminary analysis of tests including self-reported profile of mood states, indices of cognitive performance including information processing, mental speed, task measuring speed of motor performance and attentional functioning all showed an advantage to patients receiving AZT. There were no signs of AZT-induced CNS toxicity at this time.

j. Dr. Hugh Tilson presented plans for postmarketing surveillance. The sponsor plans a balanced program, with epidemiologic intelligence (spontaneous voluntary reports, field investigation, and alert reports such as the FDA serious reports, etc.) and structured studies with extended monitoring programs and collaborative studies to include continuation of existing cohorts and new cohorts such as insurance programs and HMO's.

k. Dr. Dannie King summarized the status of the treatment IND as of January 12, 1987. There were 3247 patients enrolled, with a total of 376 adverse reactions reported. Since the study is ongoing, these ADRs have not been completely analyzed. Total deaths were 97, and of those occurring in the first three weeks of therapy were excluded, there were 21. Phase I studies underway were listed, as were current or planned Phase II studies.

1. Dr. David Barry concluded the sponsor presentations noting that they believed the drug was sufficiently safe and effective for general use within certain categories of patients, and the current challenge was to define those categories more precisely. Improved survival in both AIDS and certain ARC patients, including those with neurologic symptoms and low T4 counts would seem to indicate these patients would be included. They were concerned about widespread misuse of AZT in less seriously ill patients, and were planning a program involving physician-pharmacy-patient registration in addition to label warnings.

6. The Chair opened the discussion to committee and consultant comments and questions, including:

- Was drug-induced neutropenia associated with bacterial sepsis, hospitalization or death in AZT-treated patients? Answer - No.

- Do the data indicate a differential metabolism of AZT (GAZT) in patients showing hematologic problems? Answer - There was insufficient pharmacokinetic data, but blood samples of all patients appeared to be in a fairly uniform range.

- With the shortage of AZT in the immediate post-approval period, will it be possible to initiate further clinical trials in groups such as asymptomatic seropositive people to establish if AZT will prevent progression to AIDS? Answer - such a trial is planned in conjunction with components of the Public Health Service and with the advice of the committee from the Infectious Disease Society of America, possibly beginning in May.

- What was the breakdown for types, severity and incidence of opportunistic infections between groups, and was there an indication of an antibacterial effect? Answer - The list of infections found in AIDS cases was read, and it was noted that the bulk of infections were Pneumocystis pneumonia occuring in placebo treated patients with low T4 counts. Those infections which occurred in AZT recipients were typical AIDS-associated opportunistic infections. No specific antibacterial effect of AZT was evident.

- Some toxic effects may be due to differential enzymology of cellular metabolic pools, and this may suggest a means of improving the ability of the drug to function in these pools. Reply - This possibility has been discussed, but there are no data.

- What in vitro method was used to determine anti-Pneumocystis carinii activity of AZT? Answer - One of the tests utilized steriod-suppressed rats in addition to experience in humans with PCP.

7. Dr. Robert Yarchoan of the National Cancer Institute presented data on seven patients treated with AZT, showing that four of them had some improvement in neurological manifestations with the drug. Symptomology, psychometric testing, peripheral neuropathy, dementia, delayed memory and glucose metabolism in certain regions of the brain all showed some improvement.

8. Dr. Ellen Cooper of FDA presented the Agency clinical perspective. Major strengths of the data were the highly significant differences in mortality, time to first opportunistic infections between the two treatment groups, and the fact that efficacy was supported by the other clinical data presented. Weaknesses included: optimal dosing is unclear; only 29% of 145 patients in the AZT group have been on a full dose continuously; duration of therapy in the placebo-controlled trial was short so that it is not known if efficacy will be maintained or if toxicity will accumulate with longer exposure; the range of disease studied to date is narrow; there is a paucity of animal and in vitro data; and there is the possible confounding of results due to prolonged administration of other drugs. She reminded the committee that once a drug is approved, there is no way to insure completion of preclinical and clinical studies normally required, and it is difficult to withdraw a drug. While there is strong evidence to support efficacy of the drug in the limited population studied, there are no data regarding other stages and it may become difficult to conduct controlled clinical trials to obtain necessary answers.

9. Dr. Lawrence Hauptman of FDA gave a statistical perspective of the data. His analysis of data up to the September 20 termination of the placebo-controlled study included a restratification of patients with T4 counts above or below 200 to 220 rather than 100 used by the sponsor. He stated a concern that the data were only from one study which was terminated early, and the question of how to define a population to benefit from the drug. He agreed that patients with AIDS and T4 counts under 200 would benefit, while benefit to patients with ARC was debatable, and he saw no benefit for those with T4 counts over 200.

10. Dr. Robert O'Neil of FDA raised the question of data analysis for events subsequent to September 20. At that time there were 1 and 19 deaths in the AZT and placebo groups, respectively, although every patient is now on AZT. He asked for clarification of events and a discussion of T4 counts at each time to see if they correlated.

11. Drs. Barry and King responded with a breakdown of deaths, showing that in the two weeks it required to close out the placebo controlled study there were 2 deaths in the AZT group and 4 in the placebo group for totals of 3 and 23 respectively, and in the subsequent open label study there have been 5 deaths in the original AZT group and 9 in the placebo group for current totals of 8 and 32 respectively. Most of the deaths were in the early weeks of the trial, with 6 deaths in the first four weeks after starting on AZT.

12. During the extensive discussion period, many points were brought up, including:

- The role of vitamin B_{12} and bone marrow changes seen in some patients - 20 patients on AZT experienced reductions in B_{12} levels, with 8 of these developing neutropenia or anemia, or both.

- There were no good data on drug levels versus toxicity, although dose reduction was associated with less toxicity.

- There was general agreement that incidence and severity of opportunistic infection were less in patients receiving AZT.

- There was a desire that the drug should be made more widely available, but that clinical trials should also continue so that data on the therapeutic ratio in sicker patients, those with ARC, or asymptomatic subjects would be available.

- Comments were made on continuing the NDA, a conditional approval of AZT, or a mechanism for reimbursing the sponsor for the drug, but these were not considered within the purview of the Committee or the Agency at this time.

- Concern was expressed about toxicity of the drug and how to limit potential misuse. Different labeling options including warnings and contraindications, a requirement for a consultation before prescribing, and general restrictions such as limiting its use to those knowledgable about AIDS and bone marrow suppression were mentioned. The view that physicians do read labels and that an awareness of potential toxicity would limit the casual use of AZT was expressed.

13. The Committee then took up the questions posed by the Agency, summarizing their concerns after the presentations and discussion. Questions and committee discussion points were:

a. Does the committee agree that the data from the controlled trial of AZT adequately demonstrate a significant clinical effect? Do the additional data accumulated since the end of the trial support or modify this conclusion? There was unanimous agreement that there was a significant clinical effect, although data from the open label study suggested that the initial response may decrease over time. It was noted that the data were not totally evaluable since they were still accruing.

b. What patient population has been shown to benefit from this drug? After discussion of how to define the patient population, the committee voted 10 to 1 to describe the benefitting population as those who met inclusion criteria with depressed T4 counts, PCP, and ARC patients.

c. Based on the data presented, for how long can efficacy be expected assuming chronic administration of the drug? The committee unanimously agreed that the drug had been shown to be effective treatment for 24 weeks.

d. What concerns are there about dosage? Several members stated concerns about higher, lower, decreasing, or intermittent regimens, with a unanimous agreement that they had concerns at this time.

e. Is there concern that resistance to AZT may develop? Should this influence recommendations regarding its use at the present time? There was a concensus that resistance was possible, but there were no data at this time. It was hoped that the sponsor and other retrovirologists would look for resistance and develop assays to detect it.

f. What is the concensus of the committee on the risk/benefit ratio of AZT in the patient population studied? The committee agreed that the benefit exceeded risk in patients for whom there is demonstrable efficacy, at least for the 24 week trial interval. There was also a concensus that in early ARC with more than 200 T cells, and beyond the 24 week study interval, there were no data.

g. What safety concerns remain to be addressed? Stated concerns included mechanisms of anemia, long-term toxicity, effect on gastrointestinal tract flora, and drug interactions. It was noted that the NCI intramural program had patients approaching 18 months of treatment and still on drug, and any information on toxicity will be made available as soon as it is generated.

h. If approval is recommended, are postmarketing studies of safety or efficacy indicated? After comments by committee members and the sponsor, the committee agreed that postmarketing surveillance and studies of safety and efficacy are needed.

i. Based on all the information presented, does the committee feel that AZT should be approved for marketing at the present time? Comments from committee and consultants included: a concern that there were no data on long-term use; approval of AZT would not preclude further clinical research, since the fact that it prolongs survival without curing the disease may stimulate patients to explore other therapies; the question of whether it is in the public interest to approve a drug when there are so many questions remaining; abuse of the drug may lead to unnecessary toxicity, although the risk/benefit ratio favors approval; and prevention of abuse of the drug cannot be guaranteed, but considered as part of the risk/benefit ratio. The committee voted 10 to 1 for approval of the drug.

j. If the drug is approved, based on the currently available data, how strongly should labeling address the lack of data in other population groups than the ones for which the drug will receive an approved indication? Members stated a preference for strong wording in the label, noting the great potential for toxicity; that physicians should be well versed in use of the drug, and the need for controlled utilization.

The meeting adjourned at 4:05 p.m.

(Transcripts of the open meeting may be obtained by written request to: FOI Staff, HFW-35, Parklawn Building, Room 12A-16, 5600 Fishers Lane, Rockville, Maryland 20857. Charges of 10 cents per page plus postage will be assessed by the FOI Staff. Transcripts are available for viewing at Documents Management Branch, Room 4-62, Parklawn Building, telephone 301/443-1751).