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NDA 21-036

MAR 25 1999

Glaxo Wellcome Inc.
Attn: Sherman N. Alfors
Five Moore Drive
Research Triangle Park
North Carolina, 27709

Dear Mr. Alfors:

We acknowledge receipt on March 3, 1999 of your March 2, 1999 amendment to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug and Cosmetic Act for zanamivir for the treatment of influenza.

We consider this a major amendment that will extend the review time by ninety days. The new PDUFA date is July 27, 1999.

Should you have any questions, please contact Sylvia D. Lynche, Pharm.D., Regulatory Project Manager, at (301) 827-2335.

Sincerely yours,

/S/

Heidi M. Jolson, M.D., M.P.H.
Director
Division of Antiviral Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Record of FDA/Industry Meeting

Meeting Date: July 1, 1999 **Time:** 2:00 p.m.

NDA Number: 21-036

Drug: Relenza® (zanamivir for inhalation)

Type of Meeting: Approval Issues/Labeling Meeting

Sponsor: Glaxo Wellcome

Meeting Chair: Barbara Styrt, M.D. **Sponsor Chair:** James Palmer, M.D.

Regulatory Management Officer: Sylvia D. Lynche, Pharm. D.

FDA Attendees: Heidi Jolson, M.D., M.P.H., Division Director
Barbara Styrt, M.D., Medical Officer
Stanka Kukich, M.D., Medical Team Leader
Debra Birnkrant, M.D., Deputy Division Director
Dianne Murphy, M.D., Director, Office of Drug Evaluation IV
Narayana Battula, Ph.D., Microbiology Reviewer
Walla Dempsey, Ph.D., Associate Director
Grace Carmouze, Regulatory Project Manager
Girish Aras, Ph.D., Acting Statistical Team Leader
Anthony DeCicco, R.Ph., Supervisory Project Manager
Virginia L. Yoerg, Regulatory Project Manager
Sean J. Belouin, R.Ph., Regulatory Management Officer
Daniel Boring, Ph.D., Chemistry Reviewer
Stephen Miller, Ph.D., Chemistry Team Leader
Kellie Reynolds, Pharm.D., Pharmacokinetic Team Leader
Tracey Acker, Actin Branch Chief, DDMAC
Ele Ibarra-Pratt, Regulatory Reviewer, DDMAC
Teresa Wu, M.D., Medical Reviewer
Harry Haverkos, M.D., Medical Reviewer
Thomas Hassall, R.Ph., Associate Director Regulatroy Affairs, ODE IV
Robert Kumi, Pharm.D., Pharmacokinetic Reviewer
Katherine Laessig, M.D., Medical Reviewer
Joanne Rhoads, M.D., Medical Reviewer
Prabhu Rajagopalan, Ph.D., Pharmacokinetics Reviewer
Andrei Breazva, Ph.D., Statistical Reviewer
Destry Sillivan, Regulatory Management Officer
Kuei-Meng Wu, Ph.D., Pharmacology/Toxicology Reviewer
Michael Elashoff, Ph.D., Statistical Reviewer

Lauren Iacono-Connors, Ph.D., Microbiology Team Leader
Sylvia D. Lynche, Pharm.D., Regulatory Management Officer

External Constituents: Michael Elliott, M.D., International Project Leader, Influenza
Marc Rubin, M.D., Vice President, Therapeutic Development and Product Strategy for Infectious Diseases and Hepatitis
James Palmer, M.D., Senior Vice President and Director, Group Medical & Regulatory Product Strategy
David Cocchetto, Ph.D., Vice President, US Regulatory Affairs
Janet Hammond, M.D., Ph.D., Clinical Program Head, Influenza
Michael J, Ossi, M.D., Vice President, Clinical Development for Infectious Diseases and Hepatitis
Sherman Alfors, Project Director, US Regulatory Affairs
Carmella Moody, Ph.D., Assistant Director, US CMC Regulatory Affairs
Brian Stephenson, Pharmaceutical Development
Oliver Keene, Statistics, Infectious Diseases and Hepatitis
Michele Hardy, Director, Advertising and Labeling Policy
Peter Lammers, Director, Marketing
Jim Daly, Vice President and Group Manager, Marketing

Background:

This meeting requested by the Division of Antiviral Drug Products (DAVDP) to discuss with Glaxo Wellcome the current status of NDA 21-036 (zanamivir for treatment of influenza), approval issues and selected major labeling issues.

The meeting was commenced by a statement from Dr. Jolson, followed by discussion of selected major labeling issues.

1. Summary of statement by Dr. Jolson:

Intent of statement is to clarify the objective of this meeting. The applicant has done a fine job with development of zanamivir but the actual study results are such that arguments against approvability can be made, the decision is a very close call, and the application can be considered approvable only if several conditions can be met. Two studies show activity but the third is inconclusive and does not show a positive result. Agency staff have considered prophylaxis study results as supportive in evaluating the results of the submitted treatment studies, and have evaluated the accumulated evidence in the context of the recognition that this is a difficult field to study, and with due consideration of any appropriate comparisons with the type of evidence which has supported other products which are on the market for influenza. Agency staff have also been cognizant of the public health need for new products directed at influenza. However, in viewing the results from the studies available for zanamivir, it is a dilemma to try to determine a treatment effect generalizable to a North American population, and it is suspected that any such effect is small. Conditions necessary to

support approval include the following: there must be phase 4 commitments to fill gaps in the available data (though specifics of phase 4 commitments are not being discussed today); label language has to make clear the smallness of the benefit and information about who may and may not benefit; there is a need for adequate instructions and commitment to testing and re-evaluation of these.

Summary of response from Dr. Palmer: The applicant wants to have the drug available for the 1999 influenza season, would agree to caveats/qualifiers in the label, would "do whatever we need to" post approval as phase 4 commitments. The drug has been approved in Europe, launched in Australia where the applicant consider there has been encouraging evidence of ability to use the device.

FDA: This can be a successful meeting if there is mutual understanding of what the issues are.

Applicant: Their objective from this meeting is to get close enough to move forward. In order to have a 10 week lead time before influenza season, they consider it important to have a July action.

FDA: Some of the issues could prevent an end-of-July action from being an approval.

2. Discussion of selected major labeling issues:

FDA: We will proceed by discussing the questions submitted to us by the applicant in communications of June 22, 1999, and June 28, 1999. These questions are primarily concerned with the Indications and Usage, Description of Clinical Studies, and Precautions sections of the labeling, which we agree are areas of critical concern. We are assuming the base label draft to be the version faxed from DAVDP to the applicant on June 21, 1999, because that is the most recent complete version that has been available in the same form both to DAVDP and to the applicant. We will refer to several areas where we will be proposing changes. A revised version containing these and other changes will be conveyed to the applicant soon after this meeting.

FDA: Some general statements that can be made about what is important include:

a. To convey an interpretation of treatment effects in keeping with the data viewed in the context of applicability to intended users.

b. To provide balanced information about expectations for the target population that would be likely to receive the drug with this package insert.

c. To provide full information about any safety concerns that have arisen, as even a modest safety concern may have a meaningful effect on risk-benefit balance for an individual patient.

Other issues of importance are reflected in some of the comments we have conveyed in the past; for purposes of this meeting, we will proceed by responding in order to the topics recently outlined by the applicant as key issues, which will take us in order through some points under Indications and Usage, Description of Clinical Studies, and Precautions, with brief attention to some other areas if time permits.

3. Label issues from June 22 facsimile communication

The following are some of the issues related to the label questions listed by the applicant in their fax of June 22, followed by DAVDP responses during the meeting. Additional discussion is summarized in italics.

a. Applicant asked for DAVDP thinking regarding patients "who are expected to receive adequate instruction and use the delivery system promptly and appropriately."

No efficacy data are available from any population that did not meet these qualifications. We are prepared to consider alternative placement of this information and will try to provide the best feasible alternative in our revised draft, and it probably need not appear in the Indications sentence if it can be adequately addressed elsewhere; but it appears important to convey this information because it is a defining attribute of the efficacy population.

Applicant asked also for revised wording and DAVDP indicated a version will be sent, and treatment within 48 hours will also be added to Indications, while need for instructions will be noted in Precautions and Dosage and Administration. Applicant said they are concerned with setting precedents for other drugs with similar administration and DAVDP indicated this product has enough unusual characteristics that it would not be difficult to assist in arguing that this is not likely to set a precedent for most other drugs and most others could not serve as a precedent for this one.

b. Applicant asked for DAVDP thinking regarding patients "who are judged to be in population groups likely to benefit."

In the efficacy results from these studies, while acknowledging the retrospective nature of the analyses and without claiming a statistically significant interaction effect, there were groups whose apparent benefit was sufficiently low that it appears important to make this information available to avoiding misleading impressions regarding appropriate prescribing. We are prepared to consider alternative placement of this information, as well as some re-wording of the applicable portion of the Description of Clinical Studies, and will try to provide the best feasible alternative in our revised draft. Therefore, this also probably need not appear in the Indications sentence if adequately expressed elsewhere.

c. Applicant asked for DAVDP thinking regarding indication for both influenza A and influenza B.

This area presents a real dilemma, as usually the prescriber will not know whether a patient has influenza A or influenza B at the time of prescribing. In addition, there is much less efficacy information regarding influenza B than influenza A, such that it is unlikely that an independent efficacy claim could be supported. We are in the process of evaluating whether there is an appropriate way of introducing some of this information and it is under active consideration.

Applicant indicated they think the data are supportive, and stated that "A general rule of marketing is to represent the data as it exists." DAVDP indicated a second part of Indications section is under development.

d. Applicant requested clarification of the "up to one day" statement for treatment effect, and on the role of the non-US phase 3 studies in labeling.

i. For North American studies

This is an attempt at the most generous statement justifiable taking into account phase 3 and phase 2 studies, primary and principal secondary endpoints, and lack of statistical consistency. Alternatively if they wish to propose for review a bar graph of symptom scores by day in NAIA3002, we could consider this along with clarification of how the twice-daily symptom recordings have been used to develop a single symptom score for the day, and in particular how the first few recordings have been used in patients entering the study early and late in the day. We are also giving some consideration to possible tabular presentation of NAIA3002 which could be discussed further.

Applicant wishes to discuss inclusion of data from non-North American studies.

ii. For mention of non-North American studies

The other two phase 3 studies are considered as contributing to the evidence for activity of this drug in this disease, but results of the largest phase 3 study and the totality of the evidence taken together suggest that the numerical results of the non-NA studies cannot be applied to propose a numerical effect that can be expected in NA patients, nor can the studies appropriately be combined to derive a pooled estimate because they differ in too many respects. Therefore it appears appropriate to mention them as was done in the current label draft, along with some possible contributors to differences, but it does not appear appropriate to use point estimates or any other quantitative information in such a way that it might be mistakenly interpreted as generalizable to the target population.

Applicant stated they "would be willing to do anything in terms of qualifiers, caveats, etc." and wish to present the results from the 3 studies as a range of expected effects (1 to 2.5 days). Applicant also stated they consider the EU study to be an outlier. Applicant stated they are uncomfortable because they can't explain to their other constituencies how "up to one day" was derived. DAVDP indicated to further clarify the above, applicant's analyses show a point estimate of 1.0 day difference in medians for influenza positive primary endpoint in the largest phase 3 study NAIA3002 with p=.078, NAIA2005 gives 0.75 days and p=.347, these are point estimates of one day or less and very uncompelling statistically for the only studies performed in North America with proposed marketed regimen, and principal secondary analyses suggest differences no greater and often less. Applicant objected to use of phase 2 study. DAVDP indicated the alternative is only NAIA3002 which does not demonstrate that the treatment effect "is" one day and is not compatible with a range of one day upwards, as the primary analysis did not reach statistical significance and important pre-defined secondary analyses failed to provide support. DAVDP indicated that other alternatives might be general statement such as a slight effect was observed. Applicant said they want a clear statement that will tell the practitioner what to expect, they want general principles from FDA of what is acceptable and they will put together some alternative options. FDA indicated label should convey information about effect relevant to this population, not outliers elsewhere, also subgroup analyses may be used to narrow rather than broaden intended use (applicant proposes to state certain groups have enhanced treatment effect, FDA does not see numbers to support this); also that a simple clear statement may not be achievable for a guide to physicians prescribing in North America, as there is not a clear quantifiable effect applicable to this population after exhaustive analyses (nor after the initial primary analysis alone).

e. Applicant requested clarification of the statements that safety and efficacy have not been established in high-risk population (which they say is "quite correctly" stated) and the Precaution regarding patients with respiratory disease, indicating "they seem somewhat at odds."

It's a problem that there are a number of groups in which safety and efficacy have not been established, and one of these has in addition some specific safety concerns. We propose to re-organize the Precautions section a little for clarity, but wouldn't consider it appropriate to remove information about safety concerns that have arisen, albeit from preliminary data, where these data provide information that should be made available to physicians making treatment decisions. This is particularly true because the chronic pulmonary disease population is one that many practitioners would like to treat because of the risk of influenza complications, yet little or no benefit has been shown in this population and real safety concerns have been raised which should be adequately communicated.

Applicant stated that the safety data from asthma/COPD study are preliminary, that some patients had increases in some measures, that the phase 1 study involved methacholine challenge, that they do not have sufficient information about concomitant meds etc., that

any observed PFT abnormalities just reflect the fact that asthmatics may be hyperreactive to any inhaled substance, and that they want a statement that there were no clinical correlates to the PFTs. DAVDP indicated that both in the phase 1 study and in the asthma/COPD study there were clinically meaningful decreases in pulmonary function test results which occurred disproportionately after zanamivir rather than placebo (which was also an inhaled product); that concomitant meds might obscure differences between treatment arms but in a randomized double-blinded study would be less likely to create an artifactual difference; that we will be glad to consider alternatives that are proposed, and are receiving guidance from expert pulmonary consultants on these issues.

Time constraints were noted and the applicant asked for discussion of some microbiologic (mechanistic explanation of rationale for use of neuraminidase inhibitor to be included in Mechanism of Action section) and safety (rimantadine comparison) points. DAVDP indicated an alternative statement regarding mechanistic explanation will be provided; rimantadine comparison statement was inserted because of striking similarity of AE reports between treatment arms in phase 2 study and in preliminary report from phase 3 prophylaxis study, and widespread assumption that there would be major differences; will be glad to consider proposals for alternative wording.

4. Other issues:

Applicant indicated their NAIA3005 prophylaxis study will be published in JAMA next week and there will be press release.

Applicant suggested that a statement that active-control treatment studies have not been done might address the treatment effect issues; FDA indicated this is not usually considered a necessary statement, but of course additional data that become available in the future can be considered together with (not replacing) existing data, for label revisions as appropriate. The applicant proposes to provide a summary statement regarding treatment effect; FDA is willing to consider any alternatives proposed and will also be preparing alternative suggestions.

Applicant stated they will take away a message that non-US studies are not accepted by FDA to the extent previously thought. FDA stated that on the contrary, non-US studies have been both informative and essential to this application because there clearly would not be an approvable product without them: a case for approval can be made only by considering the non-US studies as supportive of activity, although the differences in study results make it impossible to generalize the numerical magnitude of effect to the intended target population to which a US label would refer. Applicant suggested they could take the Canadian centers out of the North American phase 3 study and get a lower p value. FDA indicated the concern has been the overall results of the largest phase 3 study as it was planned and conducted, which represents the experience in the North American population, plus the phase 2 North American study which does not show better results

(again in terms of both magnitude and statistical consistency of primary endpoint effect as well as supporting analyses).

5. Identification of plans for further communication before action date.

   DAVDP will send revised comments as soon as possible, applicant will prepare alternative proposals and DAVDP has agreed to consider those.

Signature, Minutes preparer: /S/ Date: 7/27/99

Concurrence Chair /S/ Date: 7/27/99

APPEARS THIS WAY
ON ORIGINAL

Consultation Memorandum

To: Barbara Styrt, Medical Officer, Division
From: Bob Meyer, Acting Director, DPDP
Re: May 10, 1999 Response from Glaxo Wellcome for NDA 21-036
Date: 21-May-99

This is to document the consultative opinion from the Division of Pulmonary Drug Products on the new analyses and data submitted by GW in response to DAVDP's information request of March 17th, 1999 and subsequent telecon on April 1, 1999. This consult memo will only address pulmonary issues from the IR response.

1. Additional Safety Data on Influenza Negative Patients:

The safety data related to the respiratory tract (ENT/Pulmonary adverse events) do not raise any issues about the safety of zanamivir via the Rotadisk in the pivotal study population. Since this population excluded by design subjects with unstable or more severe respiratory problems, the lack of a safety signal from influenza non-affected patients exposed to zanamivir is reassuring, but only to a point.

2. Safety Data from Nursing Home Studies:

Study 3003: This study was positive-controlled, which gives a more pure answer about the tolerability and safety of the formulation than does a lactose-based placebo (which of course only answers the question of the safety of the drug substance itself). The overall upper respiratory experience in this comparative trial to rimantidine suggests some excess in vocal cord related AEs (9% vs. 4%). The overall tabulation of lower respiratory AEs does not appear importantly different between the treatment arms, in terms of cough, breathing disorders or chest sounds. However, for drug-attributed AEs, the incidence of cough is higher in the zanamivir-treated group (16% vs. 10%), as is attributed throat pain (8% vs. 5%), vocal cord disorders (6% vs. 2%) and other ENT complaints. In an open-label trial, the interpretation of these differences must be viewed with some caution, however. The only serious respiratory event during treatment was a pneumonia episode in the zanamivir group. However, there was a serious case of pneumonitis following the trial in the ramantidine group.

Study 3004: This was a placebo controlled nursing home study. In this study, the incidence of respiratory AEs during treatment was higher for active than placebo. Of note, there were excesses of throat pain (4% active vs. 1% placebo) and all lower respiratory events (7% vs. 1%). This 7% was made up of episodes of cough, 'COPD' exacerbations and 'breathing disorders'. In what was presumably a blinded-trial, none of these events was attributed to study

treatment. These data raise some concerns about some respiratory tolerability problems with the drug in this population (which presumably includes some patients with COPD and/or reactive airways).

3. Safety Data from Study 3008 (study of zanamivir in patients with asthma/COPD):

The AE experience from this study showed little important signal of poor tolerability in this population. For the AE experience during treatment, there were more lower respiratory AEs in the placebo group than in the active (27% vs. 22%) – which one would expect with an effective drug. AEs coded as asthma or COPD were approximately equal across the two treatment arms. However, there was only one episode of respiratory failure reported and it was in the zanamivir group. Interestingly, post-treatment, there were excessive lower respiratory AEs in the zanamivir group (15% vs. 12%), including slightly more asthma reports, cough reports and breathing disorder reports. However, there was one case of post-treatment respiratory failure and it was in a patient who received placebo. None of the AEs that led to study drug withdrawal was respiratory. These AE data do not suggest any clear safety problem with zanamivir (nor do they hint at any "efficacy," since the zanamivir group did not show an important decline in respiratory events relative to the "untreated" controls when the total AE experience – during and post-treatment is considered together).

Mean FEV_1 data do not show any worrisome trends, with both placebo and active showing mean improvement from day 1 to day 6 and 28. However, at day 6 (that is, at the end of the treatment period), the largest drop in the zanamivir group was 1.60 L vs. 1.02 L in the placebo group, at least raising the concern that a subset of patients show a substantial decline in FEV_1 when exposed to active treatment. A similar trend is seen at day 28 (more than 3 weeks post-treatment) with the lowest fall in FEV_1 = 1.92 L in active, vs. 0.65 L in placebo. This same kind of disparity also exists at day 6 for PEFR (largest fall in zanamivir = 143 L/min compared to 126), but not at day 28.

Most worrisome of all is the categorical analysis in table 478 of the change in FEV_1 at day six and day 28. These data show that the percentage of patients having 'significant' drops in their FEV_1s in this trial (using 20% drop as the cut-off, as would be used to define a positive bronchoconstrictive response in a bronchoprovocation test) is higher with zanamivir than placebo (7% vs. 4% at day 6, 6% vs. 3% at day 28, 9% vs. 6% at either). For patients with precipitous drops (>50%), there were 4% (3 subjects) in the zanamivir group, and none with placebo. These datat do raise concern in light of the data from the 13 patient asthma trial where 1 of 12 mild-to-moderate asthmatics who received zanamivir dropped their FEV_1 substantially in response to active treatment. The day 28 findings suggest a possibility that any deleterious effect of the drug is longer lasting rather than just an immediate increase in hyperresponsiveness. Pending more data, the safety data reviewed should, in our opinion, lead to some strong

wording in the Precautions section (and other appropriate sections) of the labeling regarding the propensity of this drug in some individuals to induce bronchospasm and/or decline in lung function. Any patients experiencing bronchospasm or decline in lung function with zanamivir should stop the drug. Further, patients should be instructed to have rescue bronchodilators available when being treated with zanamivir. Finally, pending more information, in our opinion the labeling should restrict the use of this drug to exclude patients with severe COPD/asthma.

4. PEFR data from nebulized zanamivir:

These data are only in part relevant, since the formulation is different. However, most patients exposed to nebulized zanamivir either remained stable or increased in their PEFR values. Only 2 patients out of 30 dropped their PEFR by 20% or more. Another 2 dropped their PEFRs by 15 – 20%. While the meaning of these data are unclear, it again raises the concern that some population of patients with acute influenza may have a bronchospastic response to zanamivir.

In sum, the additional information available from the sponsor again raises some concerns about the tolerability and safety of this drug product in patients with significant asthma and COPD. Given the lack of specific efficacy data to counterbalance this safety concern, it may be advisable based on the data available to restrict the indications for this drug to patients without significant and/or unstable airways disease.

If you have any further questions or issues, please feel free to call Dr. Meyer at 827-1050.

Appl_key: N021036

DRUG_NAM RELENZA (ZANAM **SPONSOR:** GLAXO WELLCOME

User: lynches **Date:** 11/5/98 3:20:22 PM **Contacted:** Bob Watson

FDA: Jim Farrelly, KM Wu
GW: Gill Dines, Jan Klapwyk, Mick Daniel, Dr. Mike Ossi, Paul Trennery, Robert Watson

Background:
Telecon to clarify issues with the rat and mouse carcinogenicity studies for Zanamivir.

Discussion:

Dr. Farrelly asked the sponsor to justify that the high doses used in both mouse and rat carcinogenicity studies on zanamivir are maximally feasible (MFD).

The sponsor stated that the high doses used were indeed maximally achievable, as the methodologies were limited by the highest concentration obtainable in the formulation and the deliverable airflow in the inhalation device.

Dr. farrelly stated that because the drug is nongenotoxic, to justify the studies using 25 fold of human exposures as a basis for the high dose would need additional information on concentrations of drug metabolites and the profile of protein binding from both studies. Dr. Farrelly said that it is more appropriate for the studies to be considered using MFD as the basis of the high dose.

The sponsor agreed to submit appropriate rationales to justify that the high doses used were MFDs.

Dr. Wu requested the sponsor to submit a summary table of tumor statistics on the rat study and to amend the missing information on toxicokinetics from both studies.

The sponsor agreed to submit all information requested, as stated above, in the admendment.

The teleconference ended cordially.

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

Record of Telecon

NDA: **21-036**

Date: **December 2, 1998**

Drug: **Zanamivir Rotadisk**

Sponsor: **Glaxo Wellcome**

BETWEEN: **Representatives of GW:**

Mr. Sherman Alfors, Manager, US Regulatory Affairs
Mr. Robert Watson, Director, US Regulatory Affairs
Michael Ossi, M.D., Director of Infectious Diseases, Clinical Research
Oliver Keene, Section Head, Medical Data Sciences

AND: **Representatives of DAVDP:**

Stanka Kukich, M.D., Medical Team Leader
Barbara Styrt, M.D., Medical Reviewer
Paul Flyer, Ph.D., Team Leader for Statistics
Michael Elashoff, Ph.D., Statistical Reviewer
Sylvia D. Lynche, Pharm.D., Regulatory Management Officer

Background:

This teleconference was scheduled at the request of DAVDP to discuss points arising from the DAVDP fax to GW of November 24, 1998, concerning NDA 21-036, and the GW draft response received by fax on December 2, 1998. These two faxes can be reviewed for background information. The following summarizes points from the discussion.

Discussion:

1. GW asked why DAVDP would want datasets from any studies other than the pivotal phase III studies and suggested there had been an agreement that only 3 datasets (from NAIB3001, NAIA3002, and NAIB3002) would be submitted. DAVDP: (1) it is noted that the NDA submission contains complete study reports with data listings from multiple studies for which data should be accessible as needed in the course of review, it is evident that datasets have been constructed to generate these reports, and asking for an electronic copy of a dataset which has already been formed and used to generate part of the NDA is a fairly minor routine request which would not ordinarily be viewed as involving any extra labor; (2) in pre-NDA discussions it was clear that electronic datasets should be provided with the initial NDA submission for any study intended for label description or salient

regulatory use (which would encompass NAIA/B2005, NAI10901, and the challenge studies as well as NAIB3001, NAIA3002, and NAIB3002), and that additional requests could follow as review commenced and progressed. GW acknowledged that it was expected datasets would be submitted for any study used in support of labeling claims.

2. It was agreed that additional data from NAIB3001, NAIA3002, and NAIB3002, and the dataset from NAIA/B2005 will be provided by December 4, 1998.

3. It was agreed that because of low enrollment thus far, it is unlikely there will be enough data available from NAI30008 for an interim report within the review timeline, but that both safety and efficacy in patients with underlying respiratory disease remain issues of major interest.

4. It was agreed that the next priority after completion of the additional data from NAIB3001, NAIA3002, and NAIB3002, and the dataset from NAIA/B2005, will be datasets from NAIB2001, NAIB2003, NAIB2007, NAIA/B2008, NAI10901, and the challenge studies. GW indicated they might be able to send these by December 23, 1998. DAVDP indicated that GW could send the files in the form they currently have with a list of variable definitions, without any additional work to make them "user-friendly", within two weeks, and that any needed modifications could be discussed in the course of review. It was agreed that an attempt would be made to do this within the next two weeks. GW asked again why the challenge studies would be wanted and DAVDP referred to pre-NDA discussions of their potential application to evaluation of influenza A versus B (in addition to the point made earlier that these are studies proposed by GW for description in the label).

5. It was agreed that additional discussion of specific contents and timeline for integrated efficacy and safety databases could take place after the individual datasets are provided, and that proposals from the applicant regarding appropriate items for inclusion would be welcome.

6. It was agreed that timely submission of data would facilitate appropriate discussions prior to the Advisory Committee meeting.

7. Two additional questions were raised by DAVDP. (1) The treatment study protocols indicate that subjects were asked to take medication and fill out diary cards at approximately 8 am and 8 pm each day, and that a second dose was to be taken on the day of study entry even if study entry (and the first dose administered at the study site) was late in the day. We would like to confirm that understanding and also confirm that it will be possible to tell in each case that a second dose was in fact taken on the day of entry. GW indicated these understandings were correct. (2) In pre-NDA discussions there was some suggestion that clinical rationales might be used to justify certain of the chemistry specifications. If that is to be done, these rationales should be provided in detail with supporting documentation and references. As these rationales and supporting information have not been found in the integrated material in the submission, our assumption is that GW considers the chemistry issues are being handled purely on the chemistry level by the chemistry group without a requirement for clinical justifications for chemistry specifications, but we would like to confirm whether this is true. GW stated this is correct.

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

Record of Telecon

NDA : **21-036**

Date: **January 20, 1999**

Drug: **Zanamivir**

Sponsor: **Glaxo Wellcome Inc.**

BETWEEN: Representatives of GW: **Sherman Alfors, Project Director, Regulatory Affairs**
Micahel Elliott, M.D., Clinical Research
Janet Hammond, M.D., Ph.D., Clinical Research
Robert Watson, Director, Regulatory Affairs

AND: **Representatives of DAVDP:** **Barbara Styrt, M.D., Medical Reviewer**
Michael Elashoff, Ph. D., Statistician
Heidi Jolson, M.D., Director, Antiviral Drug Products
Sylvia Lynche, Pharm.D., Regulatory Management Officer

Background: This telecon was requested by DAVDP to discuss DAVDP responses to the applicant's letter of January 11 and the timeline for applicant responses to DAVDP requests for information transmitted in December and early January. The telecon was originally scheduled for January 15 but ice storm & power outage forced cancellation and rescheduling.

1. DAVDP responses to GW letter of January 11:

- Desk copies of the applicant's draft briefing document for the February 24, 1999, Advisory Committee meeting were received in DAVDP on the afternoon of January 20, 1999. We will expedite turnaround to provide them with comments as soon as is feasible, and will be prepared to do the same with drafts of their slides for the Advisory Committee presentation.

- For the Advisory Committee agenda, we anticipate that the applicant presentation will be allocated approximately one hour in the first half of the morning, but details of the agenda remain to be determined; we expect it will be pretty much like the usual AC agenda. Applicant requested 75 minutes instead of the hour they proposed in their letter of January 11, and DAVDP indicated this would be considered and we will let them know.

- We expect FDA will be providing its own computer support, think they may have witnessed sharing of space rather than other resources as they describe at a recent meeting. Applicant indicated they were referring to the December AC and we confirmed that space was shared as required by room set-up.

2. Clarification of timelines and additional points for applicant responses to recent DAVDP faxes requesting information/data:

- Fax of January 6 requesting additional analyses: we appreciate their response dated January 18. This is under review, but so far we haven't found analyses of NAIA 2008 and NAIA/B 2008 comparing bid zanamivir to bid placebo instead of combined bid and qid placebo groups; this was discussed at time of protocol review and it was understood this would be provided. It would be needed for entire study and for North American component. We are looking at the phase II studies only as supportive, as they're aware, but this separation would be needed for any such use of this study; we would appreciate indication of exact location in the NDA for any such analyses already submitted, and/or provision of such analyses if not already sent. Applicant indicated they think there are some pieces of these analyses in the NDA, but not sure where, and they will get these done and provide them.

- Fax of December 18 with questions about patient instructions and use of device: we'd like to clarify timeline for when we might expect their response. With reference to this topic, it would be helpful if they could provide enough examples of the current form of the device (and placebo medication blisters?) that review team members could have them available while preparing for advisory committee and also enough to provide to AC members/consultants. We received on January 20, 1999 the patient instruction sheets they sent from other drugs using similar delivery system (Flovent Rotadisk, Serevent Diskus) and will review, but also see this drug as different because of importance of correct initial dosing in setting of acute symptomatic illness. We anticipate that demonstrating the ability of unselected dry-powder-inhaler-naïve patients to use this device correctly on the first dose will be very important; it's been a concern to us as we looked at the device, the instructions, and the investigators' comments indicating that some patients have difficulty with it even after screening and supervision; we have been consulting with Pulmonary and this has heightened the concern; depending on what they're able to provide at this point, may need to discuss whether an actual use study is warranted. Applicant indicated they are working on responses, there had been some miscommunication between their groups (regulatory, clinical, etc.) and a color patient instruction sheet is currently under development, they expect this will take a few weeks, they might be able to send us a mock-up sooner but would prefer to wait until they have the final at which time they will also send response to the other questions (except for proposed changes in the package insert portion of instructions which will accompany their response to the DAVDP fax of December 22, 1998). DAVDP indicated we would like to see their proposed instructions as soon as possible so we have as precise an idea as possible of just what the patient will be seeing, and we'd like to have this in hand as we proceed with our review; if this means sending a mock-up, they can include a covering letter saying a revised final proposed version will follow at a specified time. Applicant agreed to provide this and to send devices and placebo medication disks for review team and AC. DAVDP suggested they may also want to consider sending devices and instruction packets to AC members in advance of the meeting.

- Fax of December 22 with preliminary label comments: we'd like to clarify timeline for when we might expect their response, & will expect to review & provide more comments based on revised version. In those comments, note questions regarding influenza A vs B analyses in NAIA2005 and NAIB2005: when will these be done? Also note question about BID dosage vs two doses on first

day followed by BID: have they done an analysis of outcomes by time of day at study entry, & could they provide results? Applicant indicated they are planning to send out some responses today, haven't done an analysis of treatment effect by time of day at study entry but will provide one.

- Fax of December 23 with questions about respiratory patient subgroups: we'd like to clarify timeline for when we might expect their response. Concern is not just with potential for adverse events but also would someone whose asthma worsens in setting of acute viral infection have different distribution of drug leading to different treatment effect. Would like to see responses on this ASAP as there may be more questions in this area that would be useful (perhaps necessary) to discuss before AC. Applicant asked for clarification of why there would be any safety issue and DAVDP indicated that inhalation drugs can precipitate respiratory symptoms in some predisposed patients, some acute symptoms associated with the study drug inhalation have been described in the studies at hand, it is unclear whether more severe symptoms could be seen if a patient with underlying airways disease takes a drug which could precipitate symptoms and also has an acute infection destabilizing his/her airway hyperreactivity, and we would like to see as much information as is available to assist in evaluating this issue while awaiting more information from their ongoing study targeted to patients with underlying respiratory disease.

- Safety update: we would like to clarify date of receipt if not yet sent; again, any events in respiratory patients are of importance. Applicant indicated this is being finalized and they anticipate sending it next week; they acknowledge this is late relative to AC date. DAVDP indicated we are also interested in any information bearing on safety and efficacy in respiratory patients that becomes available later in the review period.

- Fax containing Dr. Flyer's request for information on subjects censored but not withdrawn from study: applicant indicated response was sent.

- Fax requesting more information on IRB correspondence etc. with regard to IND [redacted] applicant indicated they are working on this and expect to send response next week.

- DAVDP asked if copies of some actual filled-out diary cards could be made available to the review team: applicant said they will send some randomly selected ones from the North American and European phase III studies.

APPEARS THIS WAY
ON ORIGINAL

Concurrence:

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

Record of Telecon

NDA: **21-036**

Date: **January 29, 1999**

Drug: **Zanamivir**

Sponsor: **Glaxo Wellcome Inc.**

BETWEEN: Representatives of GW
Sherman Alfors, Project Director, Regulatory Affairs
Michael Elliott, M.D., Clinical Research
Janet Hammond, M.D., Ph.D., Clinical Research
Robert Watson, Director, Regulatory Affairs
Mike J. Ossi
Oliver Keene, Statistical
Tushar Shah
David Cocchetto, Regulatory Affairs
Patti Szymborski
Janet Hammond
Nancy Slight

AND: Representatives of DAVDP
Debra Birnkrant, M.D., Deputy Director
Barbara Styrt, M.D., Medical Reviewer
Michael Elashoff, Ph.D., Statistician
Christine Kelly, RN, MS, MBA, Project Manager

Background: This telecon was requested by DAVDP to convey and discuss comments on the GW draft Advisory Committee briefing document received 1/20/99 and submissions dated 1/18, 1/19, 1/20, and 1/22/99 containing responses to FDA requests/comments.

Discussion: The following notes summarize DAVDP comments on the above submissions, with applicant comments in Italics.

Comments on draft briefing document (these are intended to be general indications of issues they may want to consider, and are not prescriptive or maximally detailed; can schedule follow-up telecon for any outstanding issues as needed).

Microbiology/Clinical Pharmacology section: two different uses of IC50 is confusing. FDA believes most clinicians would take this to refer to inhibition of viral replication, and suggested that the sponsor may want to consider using other terms, especially to refer to 50% inhibition of activity of the enzyme. Clinical relevance for human studies of the latter is not entirely clear. On p. 29 the

statement "In summary, zanamivir resistance has not been observed in acute influenza A or B virus infection" does not evidently summarize the *in vitro* and animal data that precede it. Also note (with reference to section 7.6 which does summarize clinical trial data) that number of matched pairs appears to be less than 60 (much less if only cell culture assays are considered), rather than 300, and some decreases in susceptibility have been observed in cell culture assays – it is not clear that neuraminidase assays can be substituted for cell culture assays, and evidence can be presented comparing different resistance assays but cell culture results should be appropriately taken into consideration. ***Applicant stated they will present results from both assays and their argument for use of the [redacted] assay.***

Pharmacology/toxicology section: when a "slight" increase in lymphomas is described, the clinician may wonder what numbers this represents, and this information could be included along with the rationale for applicant's interpretation.

Proposed product: as applicant is aware, there are many unanswered chemistry issues, and it may be necessary at the Advisory Committee meeting to indicate that such issues are still under discussion; this would not require any modification of the applicable section of the briefing package.

Clinical studies: p. 62 of the briefing package states acetaminophen & guaifenesin (as Robitussin) were made available to all subjects; protocols & CSR's seem to indicate acetaminophen in all phase III studies, cough medication described as dextromethorphan in NAIA/B3002 and pholcodine in NAIB3001: FDA would like to clarify for our own information what was actually provided. ***Applicant indicated the information in the briefing package was a typographical error on their part.***

Repeated references to alleviation without relief medications as an analysis requested by FDA during the end-of-phase-II meeting: that analysis was not specifically requested during that meeting and the issue was not a new one at that time; FDA had considered some assessment of relief medications to be important to interpretation of the primary endpoint from much earlier in development (including correspondence as early as beginning of 1996 asking how relief medications would be incorporated into the primary endpoint) and reiterated this concern at end-of-phase-II meeting; it's not clear what the purpose of this reiterated reference might be. ***Applicant acknowledged the foregoing FDA comment is correct with respect to timing and content of discussions. They also stated that they feared being criticized for performing multiple analyses.*** DAVDP indicated the difficulty of taking the impact of relief medications into account in interpretation of influenza endpoints should be well understood and performing this particular analysis should not expose the applicant to criticism for performing too many analyses.

It was FDA's understanding that NAIA2005 and NAIB2005 would be analyzed as separate studies and that any combined analysis would be for exploratory purposes. FDA is uncomfortable with presentation of the combined analysis unless the separate analyses are also presented and the combined analysis noted as exploratory. FDA also has some clarification questions about these studies: p. 67 suggests that both studies used an objective temperature criterion for entry, whereas the CSR and protocol material in the NDA suggests that feverishness but not elevated temperature was an entry criterion in the first version of the protocol, and that temperature entry criterion was added to NAIA2005 after FDA review of protocol but was not added to non-IND study NAIB2005. If in

fact temperature criteria for entry were used uniformly across both studies, it's a little puzzling that one 100 out of 174 flu + patients are noted as febrile in the analysis of that subgroup; if entry criteria were not uniform, this would increase the discomfort with combined analysis. ***Applicant stated the criteria were different in the two studies and the briefing document is not accurate.*** The question of febrile patients is further confused by table on p. 82 which is labeled as an analysis of febrile patients but apparently includes some afebrile patients from A/B3002. ***After completion of briefing comment documents and before proceeding to comments on other submissions, applicant asked for clarification of this comment, stating they had performed retrospective analyses using temperature entry criteria to be consistent across all studies.*** DAVDP indicated the table on p. 82 is described as an analysis of patients febrile at entry, it includes the subset of patients febrile at entry from two studies which did not have a temperature criterion for entry, but the studies which did have a temperature criterion for entry had some patients entered who were not febrile (protocol violations) and those afebrile patients apparently are included in the table. ***Applicant indicated the table does not use consistent criteria for all studies and should be revised to do so.*** In addition it appears from the study reports that rapid/direct antigen tests were used as a criterion for flu positivity in B2005 but not A2005; as a point of clarification, FDA can't find in the data set the indication of mode of diagnosis for some patients coded as culture negative serology negative influenza positive, were these patients with positive rapid tests & can the sponsor show us where this information is in the data set or supply a corrected data set, and have they submitted performance information for these tests & can they direct us to the location of this in the NDA? ***Applicant confirmed that rapid tests were used to define the influenza positive population in B2005 but not A2005, and indicated they would provide the requested information.***

The table on p. 89 was difficult to interpret, and appears to show virology positive and serology positive patients as a proportion of all influenza positives but these tests were part of the denominator definition and it's not clear whether the virology positive and serology positive patients were the same (in which case seroconverters as % of virology positives would appear to be slightly smaller in zanamivir group for each study) – Does virology refer only to culture, or to culture, PCR, and immunofluorescence? Do they have percentages of culture-positive subjects who seroconverted? Have they compared quantitative antibody titers between treatment groups, or proportion with missing convalescent serology? ***Applicant indicated they think virology positive refers only to culture but they will have to check, they realize the table is not optimally clear, and they have performed some of the other analyses mentioned and will consider incorporating them.***

On p. 99 when AE frequencies are given for placebo subjects, can they clarify how many subjects received which placebo regimens? ***Applicant will check on this.***

On p. 109 in the ISS there was a subject in one of the prophylaxis studies who died with pneumonia positive for influenza A; here they describe a patient who died with pneumonia after developing upper respiratory symptoms during a prophylaxis study, but don't describe him as having documented influenza; were there two such deaths, or was the influenza diagnosis inadvertently omitted here? FDA would like to receive any additional information they have on this patient. ***Applicant indicated it is the same patient, they will make the briefing document consistent with the NDA, and they will send DAVDP additional information on the patient.***

Section 7.7: It is not clear why the sponsor is presenting a table of efficacy results for a study which is being reviewed only for safety (as a prophylaxis indication has not been requested in this NDA and the presentation does give the impression that data is being presented for review for an indication for which no request has been made). The sponsor might consider presenting a narrative summary of some of this information. ***Applicant indicated the presentation of prophylaxis data is intended as "proof of principle" for antiviral activity, and they are concerned they might be criticized for withholding data because the study has been presented at a scientific meeting.*** DAVDP indicated the applicant could also provide appropriate citations to the scientific meeting presentation.

Appendix 1 and throughout: In NAIA/B2008 the two placebo groups (bid and qid) are dissimilar and are not blinded with respect to one another, it was understood that analyses would be performed with each treatment regimen compared to the comparable placebo group; again, it would appear that any presentation combining the two placebo groups would be characterized as exploratory and would be supplemental to the principal (separate) analyses rather than replacing them.

Issues regarding other recent submissions & questions:

FDA anticipates being able to schedule 75 minutes for the applicant's presentation as they requested (rather than one hour as they previously requested), followed by very abbreviated clarification questions. Other AC agenda details are under discussion.

Medical reviewer would like to request more information on patient discontinued from NAIA3002 because of meningitis (can't figure out precise basis of diagnosis, or etiologic diagnosis, from case narrative; think it was subject ID 10882) as well as the patient who died with influenza A as discussed above. ***Applicant agreed to provide these.***

Statistical reviewer had questions about applicant's use of Wilcoxon test for censored data where Wilcoxon gives significant p values and log-rank test does not.

Jan 18. Submission: the sponsor provided some requested analyses and said they "would like to discuss with us any conclusions that might be drawn from these" – questions arise from concerns FDA already had about principal analyses across studies & are looking for information that would dispel some of the concerns about discrepancies between studies. Overall, in particular, FDA is having great difficulty convincing ourselves that NAIA3002 is a positive study: in the principal analyses and multiple secondary analyses it appears much less impressive than the other two phase III studies, and this is particularly worrisome because this is the largest phase III study, the only one conducted largely in the population for which we would be regulating this drug, and the only one which was both proposed initially and carried to full-enrollment completion as a principal phase III study in support of this treatment indication (FDA has incidentally had some difficulty determining from March 1998 and May 1998 submissions when decision was made to finalize under-enrolled NAIB2005, May submission may give erroneous impression that analysis was under way at that time). In the other material in the NDA and also in the additional analyses they have provided in response to our requests, FDA continues to see the pattern of North American subjects showing less treatment effect than non-North American subjects in otherwise presumably comparable protocols. This complicates the process of deciding how far data from the other studies can be generalized to the potential US treatment population. FDA considers this to be a very important issue that could

affect decisions about the drug, and needs to know how the sponsor would propose to account for these discrepancies and whether there is an explanation for the differences that is potentially correctable (e.g. patient education/instruction – see next submission discussed). Can the sponsor provide us with analyses which would explain the differences between North American and non-North American studies, and also analyses that would demonstrate lack of harm in influenza negative patients in NAIA3002 (for whom their point estimate of time to alleviation was longer on zanamivir than placebo)? ***Applicant indicated NAIB2005 was declared final because of a late-season bump in enrollment although still below original plans, and analyses did not start until July.*** DAVDP asked if they have any hypotheses to account for less effect in North American studies. ***Applicant said they have assumed Americans are more reluctant to record symptoms as improved than subjects in other geographic areas, as illustrated by adverse event reporting experience, and physician assessment at post-treatment visit showed more improvement on zanamivir.*** DAVDP indicated this had been considered but would likely have produced longer symptom course in Americans than other subjects in placebo groups, which was not the case; adverse event reporting did not differ between these studies to an extent supportive of this hypothesis for these specific populations; and for a disease in which symptoms are the primary target of treatment, if people don't know they are less symptomatic it is difficult to interpret a treatment effect. ***Applicant also indicated that AE reporting may have been decreased because events considered to be part of the course of influenza would have been reported as symptoms rather than adverse events.*** DAVDP agreed that the overlap between possible adverse events and symptoms of influenza-like illness is a problem in evaluation of influenza studies. DAVDP reiterated that we need to see analyses which would address the concerns regarding less treatment effect in North American studies, and will be glad to discuss this issue with them again before the AC depending on their response. ***Applicant indicated they will further consider these issues and they do wish to discuss them again before the AC meeting.***

Jan 19 submission of patient inserts for Flovent and Serevent: FDA appreciates receiving these and looks forward to seeing as soon as possible the one which we understand from last week's telecon is under development. ***Applicant confirmed the patient instructions insert for Relenza is under development and they hope to get it submitted soon.*** It is FDA's understanding from the treatment protocols that subjects were only entered if they could use the device satisfactorily, and that the first dose was given under supervision at the study site: please tell us if this is in fact what happened. ***Applicant confirmed this is correct.*** FDA will be interested in what plans they have for demonstrating effectiveness of the Relenza instruction insert for first-dose use by acutely ill patients who have no experience with this type of drug delivery system. FDA would also be interested in seeing any information they have on potential subjects who were excluded because they were not judged able to use the device satisfactorily, and the basis for those judgments, as we have understood they were keeping a log. FDA would also like to clarify whether the comments from physicians about incompletely punctured blisters were specifically requested or were spontaneous. ***Applicant indicated investigators were supposed to check for blisters which were not completely punctured as part of medication accountability, but there was no systematic request for recording of partially punctured versus not-at-all-punctured blisters.*** FDA is concerned because (1) there were occasional comments about inability to use inhaler or incompletely punctured medication blisters even in the study groups which had been screened and instructed (2) the instructions appear quite complex (3) their analyses showing treatment effect to be different in subjects entered before or after 36 hours suggest that someone who doesn't get it right on the first dose could thereby move from the

less-than-36-hours to the greater-than-36-hours group (4) other products using similar system appear to be for maintenance therapy in which there may be more tolerance for a learning curve and less impairment of functioning by acute symptoms when treatment is started. We consider this also to be a very important issue and look forward to their proposals for ensuring, and demonstrating, that the drug/device system is used satisfactorily from the first dose onwards in populations comparable to the relatively unselected, unsupervised, DPI-naïve, acutely ill population that would most likely be prescribed this drug in the typical primary care setting. In connection with this issue we would also be interested in whether they have information on education level and primary language of patients in the different studies. ***Applicant indicated they don't think that information was collected but will check on it.***

Jan. 20 submission with proposed label – we think our comments on the briefing document and other submissions can be taken as outlining some of our concerns about label content, and will be glad to provide more specific label comments on the version submitted here or after any revisions they may wish to make following today's discussion; they can let us know within the next few days whether they will be sending additional revisions & when. ***Applicant indicated they will let us know.***

Jan 22 submission regarding respiratory patients – point of clarification, we had asked for information especially with regard to studies in which high risk patients were recruited but unstable patients were excluded – from the ISE we would have thought this included all the principal phase III studies but the response appears to exclude the phase III studies and to include 2005 which had been described as excluding high risk patients – so we'd like to clarify just what the remainder of the response refers to, and what procedure was followed if a potential subject for a phase III study had unstable asthma at the time of enrollment, and then we can go over the response & proceed to any additional discussion that may be needed. ***Applicant indicated that despite the ISE statement that subjects with unstable chronic disease were excluded from all treatment studies, there was no specific provision to this effect in the phase III studies, and the nearest approximation was that subjects were to be excluded if the investigator believed there was a "medical condition that would affect their ability to complete the study or confound the evaluation of safety or efficacy data" (and inclusion criteria listed "able to be managed on an outpatient basis and were not medically compromised by their participation").*** DAVDP indicated it is difficult to sort out from their submission how many subjects were entered in phase III studies who actually had influenza-related instability of underlying asthma (e.g. leading to a change in asthma treatment at the time of study enrollment), and we would appreciate any additional information they can give us on such patients. ***Applicant indicated they would review their records to see if they can provide any additional information.***

Safety update has not yet arrived. ***Applicant indicated it is being shipped today.***