Appl_key: N021036

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

User: lynches **Date:** 2/8/99 3:59:54 PM **Contacted:** Sherman Alfors

FDA participants: Barbara Styrt, Debra Birnkrant, Michael Elashoff, Sylvia Lynche
GW participants: Sherman Alfors, Michael Ossi, Michael Elliott, Oliver Keene, Nancy Flack, Patti Szymborski, David Cocchetto, Janet Hmmond

This telecon was requested by DAVDP to discuss the applicant's explanations for differences between results of their principal phase III studies carried out in North America and elswhere. The telecon was initially scheduled for Friday 2/5/99 and posyponed at the applicant's request.

The applicant opened by summarizing their fax sent 2/4/99 which acknowledged that North America syudy NAIA3002 had less impressive treatment effects than their Eurpean and Soputhern Hemisphere phase III studies, and proposed their explanations for differences between North American and other studies and justifications for considering the North American study positive reasons for this difference. they also noted that their analysis of strain differences in circulation viruses was based on serology (strain was not determined for cultures) and that A/H3N2 accounted for 99% of North American and 84% of Eurpean samples.

DAVDP response: We agree that use of relief meds may be afactor contributing to differences across studies but are troubled by implications for describing treatment effect if it can be damped out by standard OTC drugs; agree protocol violations could be an issue but can't assume study would be more impressive without them; we have some difficulty with their description of why they consider presenting symptomns in North American patients to be less severe, as well as what the resulting implications for interpretation of treatment effects would be. Overall we still have difficulty seeing the North American study results as positive. We also have continuing concerns about respiratory patients regarding both safety and efficacy, not allayed by their by their additional submission. Also note we asked them to provide more information indicating no harm in influenza negatives in that study: what is their explanation for negative point estimates for treatment effect in this and other subgroups (e.g. high risk, complications in high risk, high risk influenza positive & complications therein). We need to see actual analyses supporting absence of harm where estimate of effect is negative (even with "non-significant" p value). Applicant said they will look at these groups.

They have received our request for complete report of "marketing ease-of-use study", when will it arrive here? Applicant stated they aim to send by end of week but want respond to each DAVDP question in detail. DAVDP suggested they send the complete report ASAP and their responses to specif questions can follow when they have those prepared. Applicant indicated the complete report was prepared for marketing and likely will not contain most of the information requested. DAVDP also asked applicant to verify this study did not use current instructions, as we were previously told those weren't developed until last week. Applicant said the study used the same instructions submitted last week which are also the same as the phase III studies. DAVDP noted the patient instructions from the phase III studies and those proposed for marketing (both submitted 2/3/99) have a number of differences and suggested the applicant provide the precise instructions used for each part of the ease-of-use study. Applicant agreed.

DAVDP noted sample devices and instructions received last week. In 1/20/99 telecon it was suggested that they provide a device and instruction sheet for each AC panelist, but we understand tfrom last week's comminications that they prefer the 4 devices submitted last week to be passed around among AC members. We are unclear on the focus of their comments that they are proposing to ask the AC how the device should be designed, but suggest that having the opportunity to hold the device and instructions in their hands would be useful and educational when considering clinical study results. The applicant indicated that do not want the AC to see the instructions for patients and would prefer to present an instructional session to the AC on how to use the drug/device. DAVDP suggested that most patients in practice will not have hands-on instruction and that is why the instruction sheet is important, as also stated in the applicant's summary of the ease-of-use study, but that the device could be passed around without instructions if the applicant prefers. Applicant stated that because this is a prescription drug, there will be counseling of patients by health-care providers in how to use this. DAVDP said we would be intrested in seeing any material the applicant plans to provide to halth-care providers ensuring that thsi occurs; and that we anticipate there will be more questions for discussion after we see what they are proposing to submit in the next few days.

They have received fax summarizing CAC determinations & indication that there will be a request for immunotox study. in clinical trials, it is difficult to draw any conclusions about whether there is any treatment-related difference in time to resoultion of cytopenias: can they provide any information that

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would clarify this? Applicant agreed that such conclusions may not be reachable because there were no scheduled lab draws between end-of-treatment and end-of-follow-up; DAVDP noted many of the end-of follow-up values also appear to be missing & any additional information would be welcome.

Draft slides received Friday afternoon - are under review and we will provide comments as soon as feasible. Also we will provide draft FDA slides when feasible. Applicant asked if we will provide draft review that we are sending to AC [presumably, background document]; DAVDP indicated we will have to check timeline and get back to them, but all agreed we have been making, and are continuing to make, major efforts to communicate concerns on a timely basis.

Applicant asked Dr, Elashoff if they have been penalized for submitting the European study because it appears so much more impressive that the North American results - i.e. suggested there would have been no problem if the North American phase III and phase II studies had been submitted alone. Dr. Elashoff stated that the European phase III study looks strong, and the Australian study intermediate, that North American phase II studies NAIA2005 and NAIA2008 each looked impressive than its European counterpart, and that it's more a matter of the European study salvaging the application. He stated that the North American study results are seen as a problem in how to construct label wording that would represent the study results. Applicant said they also see the issue as how to aarive at appropriate label descriptions. Dr. Styrt said that DAVDP is still grappling with the question of whether there is a treatment effect that can be appropriately descibed for the population in which USFDA would be regulating the drug.

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DRUG_NAM RELENZA (ZANAM SPONSOR: GLAXO WELLCOME

User: lynches Date: 2/12/99 10:20:48 AM Contacted: Sherman Alfors

This was a telecon with GW to discuss the CAC executive Committee report:
FDA participants: Barbara Styrt, Jim Farrell, and Sylvia Lynche
GW participants: Sherman Alfors, David Cocchetto, Paul Tiernary, Jill Dines

Dr, Farrelly outlined the reason why the CAC Executive committee felt the sponsor should conduct appropriate tests to investigate the potential immunotoxicity of this drug. Dr. Farrelly stated that although the increase in lymphomas inthe male rats in the 2 year studies was not statistically significant, there was a positive trend in the apperaance if such tumors. That, couples with the fact that there was some white blood cell effects in male rats during toxicology studies, led the committee members to question whether a decrease in immune surveillence was the underlying cause. Therefore, he said the the sponsor should conduct a study to determine the possible effect of drug exposure on T-cell dependent antibody reponse. The anti-sheep red blood cell (SRBC) IgM antibody response assay ehich has been validated by the National Toxicology Program is appropriate to be used for this purpose. Alternatively, you can use any assay of immune function for which there is a valid scientific rationale.

The sponsor thanked Dr. Farrelly and stated that they would reply with a proposal by mid March.

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DRUG_NAM RELENZA (ZANAM SPONSOR: GLAXO WELLCOME

User: lynches Date: 2/19/99 1:33:14 PM Contacted: Sherman Alfors

This was a telecon requested by GW in regards to the 2/24/99 Advisory Committee meeting. The following are DAVDP responses to GW questions in their fax of 2/16/99.

FDA participants: Barbara Styrt, Debra Birnkrant, Paul Flyer, Heidi Jolson
GW participants: Sherman Alfors, Mark Rubin, David Cocchetto, Mike Ossi, Mike Elliott

Point 1, Compostion of AC: It is our understanding that Dr. Hammer will chair this meeting. As GW is aware, it is usual (and requiring by FDAMA) to attempt to have panelists present who are expert in the disease entity under discussion, which would explain inviting influenza experts. As GW is also aware from frequent discussions before and during review, this drug delivery system is new to DAVDP and we have been consulting with pulmonary collegaues who have familiarity with other products using similar delivery systems and who would also have familiarity with some of the issues related to use in patients with underlying respiratory disease which we have also been discussing with GW throughout the review process, which would explain inviting pulmonary experts. DAVDP asked if GW had concerns about this and GW stated they did not.

Point 2, Efficacy: We have shared on multiple occasions our concern that it is very difficult to find convincing evidence of treatment effect in NAIA3002. We will not necessarily present studies as having a single numerical treatment effect. We do intend to provide copies of both background document and draft slides to GW, will try to send background document tonight if possible, and slides when feasible.

Point 3, Safety: We have shared on multiple occasions our concerns about matters such as adverse events which may be related to either drug or vehicle, about negative effects in some analyses in NAIA3002, and about pulmonary patients in particular. It additionally may be worth noting that we have concerns about the subject in the asthma tolerability study who had reproducible decline in FEV1 following zanamivir; about the subject who developed meningitis for whom the additional information submitted does not suffice to determine whether this was infectious meningitis related to the presenting symptoms or whether it could have been drug-related aseptic meningitis; about subjects listed as leaving the study due to "consent withdrawn" who may have had clinical adverse evenets and /or worsening of disease; and about the two deaths on which we asked for more information and received nothing in the recent submission characterized as a response to outstanding requests (one of which doesn't appear to be in their backgrounder? Had we better do a reconcilitation count?). [GW stated they were unaware of the death reported in the Safety Update at the time their background document was prepared. DAVDP noted the Safety Update appeared to bear an earlier date than the background document. GW acknowledged they are currently aware of it and check the completeness of their presentation.]

Point4, Diskhaler product: We do not intend to ask the Committee to draft the patient instructions, but suggest that it would be informative to invite their suggestions about education. Currently reviewing the publications alluded to in their recent submission, but from the brief summaries in the submission, neither those publications nor the marketing research study also submitted within the past week address the questions we have rasied. [GW asked if we would prefer them to give a presentation "walking the Committee through" the use of the Diskhaler. DAVDP indicated it would be useful for Committee members to be able to see and handle the device.]

Additional point, resistance/sensitivity: we can only find one paired isolate from day 5 or later. For that matter, Ican only find 39 paired isolates in their clinical virology reports from zanamivir recipients, 15 of these were only day 1 vs 2, only 22 were proposed marketed regimen. We are unable to find report RM1998/00071/00 (subjects from NAIA2005, alluded to in their background document) in the Clinical Virology section of the NDA with the other similar reports: is it located elsewhere & can they direct us to it? Also note number of mateched pairs is greater than number of subjects with matched pairs: are there other subjects somewhere we can't find, or are they counting more than one matched pair per patient in some instances? I recognize that few on-treatment or post-treatment cultures were positive in phase 3 studies, but that was true for placebo as well as zanamivir patients, so that suggests problems with method (throat swabs) rather than definitive efficacy treatment. In fact, applicant's briefing document states "The isolation rate with throat swabs was significantly lower than with nasal washings." [GW indicated they used throat swabs because that is the site of drug pressure, they did equate negative throat swabs with lack od shedding & attribute the small percentage positive to the efficacy of zanamivir compared with rimantadine even though most of their placebo subjects were also negative, they confirmed that day 2 swabs reflect about 24 hours or

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User: lynches **Date:** 2/19/99 1:33:14 PM **Contacted:** Sherman Alfors

maybe up to 36 and day 3 swabs reflect about 48 hours of drug exposure, they will have to look for information to clarify the discrepancies between number of paired specimens reported in their backgrounder and number of subjects with paired isolates in the studies reported in Clinical Virology section of NDA, andthey can locate report RM1998/00071/00 within about 15 minutes and let us know where it is.]

A little follow-up: DAVDP did fax our background document to GW about an hour after the end of this telecon, at which time no word had been received from from GW about report RM1998/00071/00.

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

User: lynches **Date:** 2/25/99 9:28:18 AM **Contacted:** Dr. Palmar

Heidi jolson received a call from Dr. Palmar, Sr. Vice President for Medical and Regulatory with Glaxo Wellcome. He called to inquire how GW should proceed following yesterday's AC meeting. She indicated the following:

GW should prepare a submission that summarizes their peespective on the meeting, including what issues were raised by the committee and how they would address these issues.

She encouraged them to consider the FDA analyses that were presented and to provide any response or comments on these analyses.

She indicated that we were in the process of preparing a request for further data analyses and additional information.

She also indicated that we would be meeting internally next week to further discuss how to proceed and we would contact them following the meeting to arrange for a face-to-face or other type of communication with them.

She emphasized that the review is still ongoing and that we consider the role of the AC as "advisory", as with any other application. Internally, we will closely examine the advice that we provided at yesterday's meeting and we will request Center-level involvement as appropriate.

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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: **March 5, 1999**

Drug: **Zanamivir Rotadisk**

Sponsor: **Glaxo Wellcome**

BETWEEN: **Representatives of GW:** **Dr. David Cocchetto, Dr. Michael Elliott, Dr. Michael Ossi, Dr. Mark Rubin, Mr. Robert Watson**

AND: **Representatives of DAVDP:** **Dr. Heidi Jolson, Dr. Debra Birnkrant, Dr. Barbara Styrt, Dr.Walla Dempsey, Dr. Sylvia D. Lynche**

Background:

This teleconference was scheduled at the request of DAVDP to discuss points arising from the February 24, 1999 Advisory Committee Meeting and a letter dated March 2, 1999 from Dr. James Palmer (Vice President , Glaxo Wellcome) . The teleconference also responded to a Request for a Meeting contained in the letter of March 2, 1999, from the applicant. The following summarizes points from the discussion.

Discussion:

1. The timing of the transmission of the DAVDP background document and slide copy to the applicant was clarified: this timing reflected the fact that DAVDP has fewer resources and personnel that can be devoted to preparing presentation material tan the applicant, and therefore was not able to have such materials prepared as far in advance as the applicant. The timing did not reflect any intention of withholding information. GW received the backgrounder and presentation material as soon as it was finalized.

2. Independent of the timing of transmission of backgrounder document and slide copy to the applicant, it was acknowledged that the applicant may have been taken unawares by some elements of the presentation itself, and that DAVDP did not intend this to happen and is undertaking steps to avoid this happening in the future.

3. The reasons for the composition of the Advisory Committee panel were discussed, including the fact that three influenza experts were present because there are supposed to be at least two experts on the disease under consideration and there have been multiple recent problems with experts being disqualified or canceling on short notice (including some who were invited for this meeting but proved to have conflicts of interest); the presence of pulmonary experts with experience related to the use of similar delivery systems was included because of the novel drug delivery system for an antiviral; and the presence of several individuals who either are in the process of joining the Antiviral Drug Advisory Committee or have voted with this Committee in the past and were substituting for absent members (statistician and consumer representative). All had experience that would be expected to confer familiarity with regulatory issues. It was acknowledged that Committee members having to leave for the airport is a frequent problem on the last (or only) day of any Advisory Committee meeting and may need to be addressed by Advisory Committee staff, but that all members on this occasion did stay through the initial discussion and vote.

4. The role of pulmonary consultation was clarified as being related to use of the device/delivery system which is new to DAVDP but familiar to the Division of Pulmonary Drug Products in its use with other drugs approved in that Division, and to assessment of primarily safety concerns regarding use of this drug by patients with underlying respiratory disease which had been noted throughout development.

5. The role of FDA pre-review of applicant's draft background document and slides was clarified: FDA reviews these materials to ascertain that salient issues are covered in an accurate fashion but is not responsible for ensuring their maximal effectiveness of presentation style, which is the responsibility of the applicant.

6. The review of this NDA is viewed as ongoing and it was agreed that both DAVDP and the applicant find it appropriate to consider extending the clock on the basis of a major amendment which may be either the Chemistry amendment just submitted or the response to a multidisciplinary letter of request for additional information currently being prepared by DAVDP. It is expected that this letter will be sent during the next week or so and contents may include requests for additional analyses and/or a revised organization and presentation of existing efficacy analyses, plus new safety and virologic information that may be available from ongoing studies, and an overall update on the enrollment status of ongoing studies. The purpose of this information request is to provide GW an opportunity to respond to issues raised by the Advisory Committee. It was specifically mentioned, and clarified in response to a question from the applicant, that additional pulmonary function tests including in-clinic pre- and post-dose spirometry from the ongoing study in patients with underlying pulmonary disease may be an important contribution. Chemistry and patient/provider issues may also be included, and additional requests may follow. There was brief discussion of endpoint issues; the pre-defined primary endpoint remains of major interest although supplemental analyses may be useful in refining the interpretation of the primary analysis, and both the applicant and DAVDP intend to perform further analyses of any evidence of a pattern of symptom recrudescence. The applicant was encouraged to include in their response to the letter any additional material that they believe addresses concerns raised at the Advisory Committee meeting; they stated that they have begun to

prepare responses to some of the issues from the meeting.

7. The ongoing review may include transmission to the applicant of comments on the proposed label. Providing such comments does not carry any implications regarding a regulatory decision and does not indicate that any such decision has been reached. DAVDP does not expect to take this application to another Advisory Committee meeting on the basis of additional information discussed in this teleconference, but would seek input at Center level within the FDA if it appears that the aggregate information may support approval.

8. Applicant stated they appreciated the clarifications. DAVDP indicated willingness to meet with the applicant at any time and asked what the applicant's preferred timeframe for a meeting would be in light of the discussions taking place during this teleconference. Applicant stated they would defer their meeting request until they receive and review the letter of request to be sent by DAVDP, and they will confirm in writing that the request for a meeting has been deferred. GW ad FDA acknowledged that a separate meeting to discuss CMC issues may also be indicated.

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: **April 1, 1999**

Drug: **Zanamivir Rotadisk**

Sponsor: **Glaxo Wellcome**

BETWEEN: **Representatives of GW:** **Dr. David Cocchetto, Dr. Norma Collingsworth, Dr. Michael Ossi, Dr. Mark Rubin, Dr. Nancy Flack, Mr. Sherman Alfors Dr. Michael Elliot, Dr. Janet Hammond**

AND: **Representatives of DAVDP:** **Dr. Heidi Jolson, Dr. Stanka Kukich, Dr. Barbara Styrt, Dr. Sylvia D. Lynche, Dr. Robert Meyer, Dr. Dan Boring**

Background:

This teleconference was scheduled at the request of DAVDP to discuss the GW's letter dated March 30, 1999, regarding NDA 21-036 (zanamivir for inhalation for treatment of influenza). It also provided further follow-up to GW's fax dated March 24, 1999, in addition to the telephone conversation between Dr. Sylvia Lynche of DAVDP and Dr. David Cocchetto of Glaxo Wellcome on March 25, 1999, which was the initial response to that fax. The following summarizes FDA comments on GW's letter and fax; GW's responses in the teleconference are summarized in italics.

Discussion:

DAVDP: Would like to review issues because GW's letter of March 30 and fax of March 24 suggest that they viewed the DAVDP letter of March 17 as an attempt to collect further information in support of non-approval of the NDA. This was not the intent of the DAVDP letter of March 17, which should rather be viewed as offering GW an opportunity to make the best possible case for their application and to participate in trying to construct an argument for approvability. It is unclear (and not possible to predict) whether such an argument can be successfully constructed but if it can be, input from GW would be necessary.

GW: *Requested specification of items needed for approvability.*

DAVDP: would need overall understanding of differences between studies, confidence and comfort level regarding interpretation of treatment effects and their differences, confidence that patients can be adequately instructed and use the product appropriately; would need to have enough information supplied with adequate time for review, as material submitted late in the review process may not be able to make a constructive contribution.

DAVDP: Overall discussion will follow the sequence of the March 30 letter and comment on highlights where it may be possible to clarify reasons for a request or receive clarification from GW regarding time and feasibility requirements. This process will also cover points raised in the fax of March 24, so a separate point-by-point discussion of that fax will not be carried out in the interests of time. It is anticipated that not all issues can be covered, let alone settled, in the time available for the teleconference, so additional questions and discussions may follow over coming weeks.

Clinical subgroup analyses (section IA1 of letter, and general comment on analyses requested): It may be useful to clarify that many of the analyses requested in the DAVDP letter of 3/17 were analyses that appeared to have been done already in various parts of the NDA submission, for which we consider it would be useful to see presentations using endpoints and subgroup analyses that are consistent across studies, in the hope of being able to evolve a description of treatment effect that is applicable to the populations under consideration in a reasonably uniform way. In some instances this may involve partitioning of subgroups to achieve consistency across studies, but in most instances not fundamentally new analyses. We have tried to suggest a pattern of analyses that would permit a coherent description of efficacy and safety for relevant populations across studies to the extent permitted by the data. We would appreciate some clarification of the time this is expected to require before results are submitted, as it would be very important to have adequate time for review after receiving these.

GW: *Acknowledged that most of the analyses were already done in the preparation of the NDA, that their letter indicated a conservative timeframe and many of the items could probably be prepared sooner.*

DAVDP: (Comment on section IA1a)Age groups were suggested partly on the basis of breakdowns already used in the NDA and also to try to have enough subjects in each group across studies for evaluation. Temperature cutoff at 38.3 was suggested because it should permit some assessment of relationship between temperature at initiation of treatment and treatment effect for all treatment studies and corresponds to one of the principal conventional definitions of clinically significant fever (101 F). Symptom duration cutpoint at 24 hours was suggested because subjects with more than 36 hours of symptoms were not eligible for NAIB3001 and we had understood from GW's previous statements that timing in NAIB3002 was collected only as first 24 hours or second 24 hours: therefore, it was our impression that a comparison of 36 hours or less versus more than 36 hours would not generate useful information for 2 of the 3 principal phase 3 treatment studies, but that using 24 hours as the cutpoint would permit some assessment of relationship between symptom duration at initiation of treatment and treatment effect, using uniformly defined subgroups, for the 3 principal phase 3 treatment studies plus whatever other studies had this information available. If this is not the case we are glad to have the issue clarified.

GW: *Stated they do not have any information for partitioning symptom duration at entry for NAIB3002. It was agreed that they will consider whether there is a time breakdown that would permit looking at earlier vs later treatment within study for a maximum number of studies while also looking at uniformly defined early-treatment groups across studies, and provide this information for further discussion.*

DAVDP: (Comments on section IA1b and IA1c) Analyses such as time to alleviation/eradication without relief medications and without subsequent symptom rise were suggested partly in follow-up to their submission of January 18, 1999, in which they provided some time to alleviation without recurrence and time to eradication analyses in response to DAVDP fax of January 6, 1999. It was our impression that these exploratory analyses of time to eradication might show point estimates of treatment effects in NAIA3002 more in keeping with the other studies (although still with less impressive p values) than some of the other analyses. We had therefore suggested these analyses as part of the effort to find common ground between NAIA3002 (and North American results in general) and the other studies, as there has been general concern among reviewers about the lack of convincing treatment effect in NAIA3002. We do consider it important to have a shared understanding that, as discussed previously, it is very difficult to find any convincing treatment effects in NAIA3002, and consider secondary analyses extremely important for support of any marginal effect that can be descried in this study. However, there is no intent to try to elicit any analysis that GW is uncomfortable with or believes should not be done. The analysis of a total symptom score by day was suggested because it has some analogies to analyses employed in some studies of amantadine and rimantadine. Such analyses would not replace the principal analyses but would facilitate any attempt to determine whether results of the zanamivir studies, even where they may appear marginal, might compare favorably to studies of previously available influenza drugs.

GW: *Stated they will provide the analyses referred to in these two sections.*

DAVDP: (Comment on IA2): Analyses of subjects with rise in symptoms after initial satisfaction of alleviation criteria: applicant and FDA have previously agreed that it is important to be able to document that detailed attention has been paid to these issues. We have suggested some ways of developing such documentation and will be glad to review what GW submits.

DAVDP: (Comment on I A3 and 4): time of submission will affect the ability to include these results in review; GW has indicated that use of relief medications may be important in explaining differences between studies, and any systematic examination of the effects on endpoints and treatment effect may be important.

GW: *Stated they may be able to submit results earlier than initially projected.*

DAVDP: (Comments on section I C, patients with pulmonary disease: Dr. Meyer from Division of Pulmonary Drug Products participated in this discussion as a consultant to DAVDP) GW's impression that Advisory Committee panelists did not think further information was needed in this population may have been due to the fact that much of the Advisory Committee discussion focused more lengthily on efficacy issues; DAVDP does not agree that no safety concerns were raised regarding pulmonary patients, and considers this to be an important safety issue in the review process. A number of panelists expressed a need for more information in this patient population, as have our internal pulmonary consultants. This includes the acquisition of more information on the possibility of acute post-dose PFT changes in acutely infected patients (as already discussed) and the expansion of efficacy information if possible (hence our suggestion to discuss feasibility of formal interim analysis), both of which would most reasonably come from NAI30008. Although updated safety data is of greatest immediate importance, if an interim efficacy analysis appears feasible this could potentially make an important contribution to risk/benefit calculations in this population, and GW may wish to consider feasibility issues and engage in further discussion of this possibility. We would also like to request clarification of GW's definition of asthma exacerbation in this study, regarding use of prn bronchodilators and how they are accounted for when determining whether an exacerbation requiring medication increase has occurred.

GW: *Indicated that subject's medication card recording of prn medication use and physician's impression of exacerbation are both taken into account in the definition. GW also asked for clarification of the requests for PFTs near the time of dosing and suggested that the protocol-defined end-of-treatment FEV1 should provide sufficient information, while addition of PFTs around the time of dosing would be cumbersome and might not be well accepted.*

DAVDP: Dr. Meyer indicated that the phase 1 study in non-infected subjects did not raise major concerns regarding long-term PFT consequences but did show decreased FEV1 immediately after dosing with active drug but not placebo in one subject, and the report of URI symptoms in that subject was consistent with the concern that acutely infected patients might be at risk for immediate post-dosing effects. He suggested that a subset of patients could be studied and post-dose FEV1 could be measured over the first 15 minutes, with longer follow-up only if decreases from pre-dose were seen during this time period.

GW: *Indicated they would consider whether this could be done as a separate study in persons with influenza.*

GW: Looking for any additional source of information on immediate effects of zanamivir on PFTs, the CASG study appears to be one of the few possibilities with some information already collected; although we know this study is under the purview of NIH and uses the nebulized formulation of zanamivir, it does appear to incorporate at least pre- and post-first-dose PEFR, and the study is cited and summarized in the NDA, the applicant would apparently have the possibility of requesting additional information from the NIH and submitting it to us as supportive, and we invite GW to do so in order to provide as much of the needed reassurance regarding this patient population as possible.

GW: *Indicated 24 subjects were entered in the first year and have clean data available, perhaps 14 more have data that can be put into clean form from the second year of the study. It was agreed that although the numbers are small this would represent a larger number of influenza-infected subjects with PFTs around time of drug exposure than currently available, that submission of the first year's data could be expedited with the second year's data to follow, that unblinding could be discussed subsequently if there are any findings that so warrant.*

DAVDP: Section I D, minor clarification regarding NAIA3004 which is not a principal subject of telecon and will be dealt with separately: their covering letter states they are continuing it in the Southern Hemisphere, we were under the impression it was being conducted only in Lithuania.

GW: *Applicant indicated they are planning expansion to Southern Hemisphere and will provide relevant submissions soon.*

DAVDP: Section I E, other safety issues. Influenza negative subjects: we have previously expressed our concern about findings in influenza negative subjects, which we do consider to be a safety issue. We are unclear as to why it is not feasible to provide results for each symptom (this is same analysis done in NDA for ITT and influenza positive groups), and would like to clarify the timeline.

GW: *Indicated they can provide the analyses, their proposed May 10 submission was due to considering this a low priority, and they will evaluate the situation further.*

DAVDP: Immunocompromised: note the AC concern regarding resistant influenza B isolate arose from a published case in a major journal which had aroused concern before the meeting, as showing that resistance can occur in a population likely to be treated.

GW: *It was agreed that principles of compassionate use availability can be discussed separately.*

DAVDP: Section II, Virology issues: We look forward to seeing the quantitative virology and resistance data summaries and proposals requested for purposes of ongoing review. We are interested in cross-resistance data, and in any discussions of neuraminidase inhibitors as a class; as they are aware, this is the first neuraminidase inhibitor to reach this stage in the review process, and we are not singling it out as uniquely a target of resistance concerns but there are not other class members at a stage to be included in comments at this point. With regard to NAIA3005, we are requesting the electronic dataset in order to have the opportunity to replicate GW's analyses in this NDA review.

GW: *Stated they appreciated the clarifications.*

DAVDP: Section III, Chemistry issues: In general, the items requested were thought to be already done or readily available, so clarification on timelines and lack of availability would be appreciated. DAVDP believed it had been agreed that continued updating of the original stability batches would be made available in addition to information on the subsequent batches.

GW: *Indicated that had not been understood.*

DAVDP: Indicated the information requested in IIIB parallels information routinely provided to the Division of Pulmonary Drug Products and it was expected the applicant would have performed the tests and only need to provide a report.

GW: *Indicated they had not performed those tests.*

DAVDP: Indicated it is usual for a rationale to be provided when an applicant proposes deviations from the guidance standards with which the applicant is familiar.

GW: *Indicated they will not be ready to provide their rationale until they do more tests.*

DAVDP: Iindicated the proposed submission times leave very little time for review even with the extended PDUFA date.

GW: *Indicated they may be able to send information earlier in installments.*

DAVDP: Use and instruction issues: The principal comment at this stage is that we consider these issues important, we need to see satisfactory progress on this issue, and we look forward to receiving their proposals as soon as possible. We may not necessarily need to see completed studies in this area before determining an action in the short term, but need to be satisfied that adequate movement in that direction has occurred.

GW: *Offered to submit their protocols simultaneously to DAVDP and DDMAC, and it was agreed that both Divisions would need to see these protocols and sending them directly to both might be useful in management of review time.*

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: **May 14, 1999**

Drug: **Zanamivir Rotadisk**

Sponsor: **Glaxo Wellcome**

BETWEEN: **Representatives of GW:** **Dr. David Cocchetto, Dr. Norma Collingsworth, Dr. Michael Ossi, Dr. Mark Rubin, Dr. Nancy Flack, Mr. Sherman Alfors Dr. Michael Elliot, Dr. Janet Hammond, Dr. Carmella Moody, Dr. Patty Szymborski, Dr. Oliver Keene, Dr. Don Kellerman**

AND: **Representatives of DAVDP:** **Dr. Heidi Jolson, Dr. Stanka Kukich, Dr. Barbara Styrt, Dr. Sylvia D. Lynche, Dr. Dan Boring, Dr. Debra Birnkrant**

Background:

This teleconference was scheduled at the request of Glaxo Wellcome to discuss the questions regarding recent submissions to NDA 21-036.

Discussion:

The applicant opened the teleconference with a statement that one more clinical submission is planned in addition to the chemistry submission planned for June. The additional clinical submission is projected for May 20 and will contain analyses of relief medication use and multivariate analyses. Dr. Boring asked whether the CMC material to be submitted in June would be in a format compatible with the available software and the applicant stated that this would be arranged. The applicant asked whether there were any issues regarding the Labeling and Nomenclature Committee submission of the Rotadisk labeling submission and Dr. Boring indicated that none had been noted.

The following two items were proposed for discussion in the applicant's telephone facsimile communication requesting the teleconference.

1. We have tried to be constructive in tone and content in the submissions throughout the month of April. Were the content and format of these submissions in line with your expectations?

2. We believe that we have thoroughly and fully addressed three of the key issues affecting regulatory decision making on zanamivir (i.e., "recurrence" of symptoms, information on the treatment effect of zanamivir, and a proposed program to monitor for viral resistance). Has your review progressed to the point where you are comfortable stating whether you agree or disagree that we have put these key issues to rest?

The following are summaries of DAVDP responses to these items, with some additional discussion indicated in italics.

We are in the process of reviewing the overall collection of submissions, which has extended up into May with the most recent received just a few days ago. As we're all aware, there is not a pre-specified list of key issues that can be crossed off the list and put to rest, as we have to consider the totality of the data. We have received a substantial amount of material in response to the issues raised in the letter of March 17 and are actively reviewing what we received. It would not be appropriate to state any conclusion from this review at this time point especially with submissions still ongoing, as we have to review the submissions in context, and there is always the possibility of concerns arising or re-emerging as review progresses. A few comments can be made on some specific points on which the applicant asked for input, but these should not be considered as comprehensive. We'll also indicate some steps we are taking to try to further a shared constructive approach to some of these points.

a. With regard to symptom "recurrence": it appears to be generally acknowledged that there can be fluctuation of symptoms to some extent after the protocol-defined primary endpoint is reached. It would probably be best to have this explicitly acknowledged in the review and potentially in label language. The additional information on this point submitted by the applicant is being carefully taken into account.

b. With regard to treatment effect: we continue to be concerned by the lack of convincing demonstration of treatment effect in the largest phase 3 study (and in certain high-risk subgroups such as underlying pulmonary and cardiovascular disease, especially in NAIA3002) and by the difficulties of deriving a meaningful generalizable description of treatment effect (especially considering the differences between studies and between subgroups). Among the active issues pertaining to this problem, without implying any regulatory decision, are the following:

i. We have been working on label comments attempting to try out how current understanding of treatment effect could be incorporated into label language. We anticipate that some suggestions for revisions of the current draft will be transmitted soon; note that additional comments and suggestions for revision may be made in the course of ongoing review.

ii. We suggest that study of improvements in patient instructions should be seen as an opportunity to demonstrate that a more reliable treatment effect might be produced after improvement of the instructions. Our comments on the first draft of the applicant's proposed label comprehension study have been conveyed separately.

iii. It has been agreed that education of health care providers may also be important to maximally effective use of this drug/device/delivery system, and we suggest that there is also an opportunity to explore effect of such education on treatment outcomes. With regard to their recent comments on their plans for healthcare provider education, we would appreciate any more specific information that can be provided on proposed content and methodology of their educational program and plans for monitoring its effectiveness.

iv. There are a couple of points on which clarification would be useful. For example, when looking at risk factors for greater or lesser treatment effect, we still have some confusion about analysis by duration of symptoms at entry in B3001 and B3002. Although it is now stated that such analyses cannot be conducted for these two studies because the information was not collected [*applicant confirmed this*], Dr. Elliot's comments at the Advisory Committee meeting clearly suggested that some information of this sort was known for both studies and that relationship to treatment effect had been examined by the applicant for B3001; in addition, B3001 study report has a table of this information. Can they clarify what was measured and how it does or does not contribute to analysis? *Applicant indicated they do have information on symptom duration before study entry for B3001 and would be able to analyze treatment effect for entry before versus after 24 hours of symptoms for B3001 and A3002; they asked why DAVDP wants it. DAVDP indicated as in previous discussions, it may be useful to know what can be documented about earlier versus later treatment using similar definitions in more than one study, as the current analysis of before-and-after-36-hr in A3002 apparently can't be duplicated in either of the other phase 3 studies. They can add cautions about the level of uncertainty etc. Applicant stated they will provide the before versus after 24 hour analyses.* As another example, Attachment 3 of April 23 submission appears to have no lower respiratory events in B3001 placebo recipients: should it be assumed that there were none? *Applicant stated they just discovered this table was missing and will send it immediately.*

c. With regard to resistance monitoring: we note they indicate a plan has been drafted and is under discussion with various agencies. We would appreciate any additional information they can provide such as copies of the current draft plan, information on ongoing discussions (including proposals for where testing will be performed), etc. We would also appreciate any virologic information they can provide from their ongoing nursing home studies, even if blinded. In general terms, we continue to have the concerns expressed throughout the review process regarding the complementary usefulness of different specimen types (e.g. throat swabs and nasal washings) and tests of drug susceptibility (enzyme-based and cell-culture-based).

That is, if there is no reliable test for resistance at the cell-culture level, conclusions regarding non-detection of resistance will be extremely limited; if culture sampling is done using methods known to have much lower yields than other methods, conclusions regarding cessation of shedding will be extremely limited. These issues will have to be taken into account in the interpretation of data. We agree with applicant's suggestions in their April 7 submission that samples may be stored for re-assay when better methods are available and that there are settings in which use of more than one type of specimen (e.g. throat swab and nasal washing) might be appropriate. There will be additional comments on virologic issues as review of any provided information progresses. *Applicant stated some isolates from nursing home studies have been submitted for resistance testing but it will probably be more than a month before any results are available. It was agreed that applicant will indicate what their timeframe might be for providing any of this information and there may be discussion of whether that could fit into the review timeline; however, any information received too late for the ongoing review will not contribute to the outcome.*

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: **June 25, 1999**

Drug: **Zanamivir Rotadisk**

Sponsor: **Glaxo Wellcome**

BETWEEN: Representatives of GW: **Dr. David Cocchetto, Dr. Norma Collingsworth, Dr. Michael Ossi, Dr. Mark Rubin, Dr. Nancy Flack, Mr. Sherman Alfors Dr. Michael Elliot, Dr. Janet Hammond, Dr. Patty Szymborski, Dr. Oliver Keene**

AND: **Representatives of DAVDP:** **Dr. Barbara Styrt, Dr. Sylvia D. Lynche, Dr. Debra Birnkrant**

Background:

This teleconference was scheduled at the request of Glaxo Wellcome, principally to discuss the draft agenda that Glaxo Wellcome proposed for the meeting proposed by DAVDP for July 1, 1999.

Discussion:

The following numbered topics are the bullet points listed by the applicant, in their telephone facsimile communication of June 22, 1999, for discussion in the teleconference. DAVDP responses follow each one. Additional discussion is summarized in italics following the question and response.

1. We would like your agreement that this draft agenda is acceptable. Alternatively, we will be happy to receive your changes to the agenda.

We anticipate a statement by Dr. Jolson immediately following the introduction of personnel at the face-to-face meeting. Then we expect we can proceed to discussion of some major label issues. The expectation is not to finalize label language in this meeting but to facilitate discussion of some of the major issues.
Applicant asked if it would be acceptable to schedule 5 or 10 minutes for Dr. Jolson's introductory statement. DAVDP indicated that planning for 10 minutes would be reasonable.

2. The agenda is focused on clinical and regulatory topics. Please note that we have not reserved time on the agenda for topics in the CMC, nonclinical toxicology, virology, or statistics areas. Please let us know if the review team wants to reserve time for specific topics in one or more of these areas.

We expect that some of the major label issues will be discussed, that discussion may be limited by the time available, and it cannot be expected that all issues will necessarily be discussed nor that language will be finalized within the timeframe of the meeting. *It was agreed there may be follow-up teleconferences and other communications after the meeting. Applicant indicated they will have personnel from other review disciplines also at the meeting.*

3. Our intent is not to submit additional draft labeling before the meeting on July 1, but rather to come prepared to discuss the review team's draft labeling of June 21. We trust that this approach is acceptable.

It's their decision whether to submit additional material before the meeting, and of course DAVDP may also have additional comments at the meeting. Also of course, anything they are able to submit in advance may facilitate discussion. *Applicant indicated they sent a submission yesterday responding to a DAVDP inquiry of May 17, 1999, about adverse events.*

4. Pages 3-4 of this fax summarize the most important issues for discussion on July 1. We would benefit from hearing your current thinking on these issues during the teleconference.

We appreciate the list of issues particularly important to the applicant. It appears most appropriate to defer discussion of specific label points to the meeting itself. As the applicant is aware, of the various issues of concern to DAVDP, achieving an appropriate description of treatment effects as they become apparent in the review is among the major ones.

5. Once we complete our discussion on these most important issues on July 1, we propose to use any remaining discussion time to discuss other less critical labeling topics. We trust that this approach is acceptable.

As noted, we anticipate that most of the discussion time will be devoted to the principal issues and that these and other issues may still require some follow-up discussion after the meeting. Therefore, what is included may depend in part on how much time is occupied by the principal issues.

Applicant asked whether there are other issues considered important by DAVDP, in addition to those listed in applicant's fax of June 22, 1999. DAVDP indicated that many issues of importance are reflected in the label comments that have already been sent, there may be additional label comments from DAVDP at the meeting as we assume that label issues will be discussed both at GW and at FDA between now and the meeting, and that our assumption is that the items listed by the applicant are those to which the applicant wishes to devote principal discussion time based on their review of the prior FDA comments. DAVDP further noted that most of the applicant's concerns appear to be focused on Indications and Usage, and that the applicant may wish to consider the opportunity to submit their proposals in the coming week. Applicant said they are concerned that label revisions might cross in the mail or arrive too late for review. DAVDP indicated the applicant is welcome to fax proposals with a hard copy to follow, that anything arriving too late for full review before the meeting obviously cannot receive complete consideration before the meeting, but we will be glad to give whatever time is feasible to consideration of any items received in the interim, and this could be useful for any issues on which the applicant wishes particularly detailed discussion.

Applicant mentioned they have been told that the projected meeting with Dr. Lumpkin was cancelled due to a time conflict. DAVDP confirmed this information conveyed by DAVDP previously, and noted that Dr. Lumpkin has the background material and is well-informed. Applicant agreed to send a list of anticipated meeting participants.

Appl_key: N021036

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

User: jolson **Date:** 6/29/99 1:21:10 PM **Contacted:** Dr. Palmer

I received a call from Dr. Palmer of G-W, re: Thursday's face-to-face meeting re: labeling. He called to briefly discuss the objectives of the meeting, and also to convey his perspective re: description of the trial results. Incorporation of the numerical data from all three trials is of primary importance to the company. He also requested permission to include marketing representation at the meeting.

I indicated that the meeting would be an opportunity for both sides to convey their perspective on the critical labeling areas, including "indication", precautionary information in asthmatics, and the description of the trial results. Participation by marketing would be welcome at the meeting.

Heidi

APPEARS THIS WAY
ON ORIGINAL

Appl_key: N021036

DRUG_NAM RELENZA (ZANAM SPONSOR: GLAXO WELLCOME

User: jolson Date: 7/13/99 12:36:34 PM Contacted: Dr. Palmer

I received a brief call from Dr. Palmer re: the status of ongoing labeling negotiations on the pending NDA. I indicated that GW would soon receive a revised label back from the division, as well as a proposed list of phase IV commitments. He reiterated the company's willingess to agree to anticipated phase IV requests.

APPEARS THIS WAY
ON ORIGINAL

Appl_key: N021036

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

User: lynches **Date:** 7/20/99 4:31:56 PM **Contacted:** Sherman Alfors

A fax was issued to Glaxo Wellcome regarding revised labeling comments and revised draft phase 4 commitments. Sherman Alfors was given a call to let him know that a this information was being sent . He was not available so a message was left. I inform him that it would be appreciated if this information can be return quickly and that it was also being sent by e-mail.