CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21036

ADMINISTRATIVE/CORRESPONDENCE DOCUMENTS

GlaxoWellcome

October 20, 1998

Mellon Bank
Food and Drug Administration
Three Mellon Bank Center
27th Floor (FDA 360909)
Pittsburgh, PA 15259-0001

Re: NDA 21-036; RELENZA® (zanamivir for inhalation)
User Fee: With Clinical Data
User Fee [redacted]

Please find enclosed Glaxo Wellcome check number [redacted] in the amount of [redacted] This payment is [redacted] of the application fee for the New Drug Application listed above. This application will be filed on October 22, 1998 to FDA Center for Drug Evaluation and Research, Division of Antiviral Drug Products.

Please find below requested information regarding this application.

Type of Application:	New Drug Application with Clinical Data	X
	New Drug Application without Clinical Data	
	Supplemental New Drug Application with Clinical Data	

Should you have any questions, please contact me at (919) 483-6030. Thank you.

Sincerely,

Sherman N. Alfors
Project Director,
Regulatory Affairs

Glaxo Wellcome Research and Development
Five Moore Drive
PO Box 13398
Research Triangle Park
North Carolina 27709
Telephone
919 248 2100
A Division of
Glaxo Wellcome Inc.

EXCLUSIVITY SUMMARY FOR NDA # 21-036 SUPPL #____

Trade Name Relenza® Generic Name zanamivir for inhalation

Applicant Name Glaxo Wellcome HFD # 530

Approval Date If Known _____

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it an original NDA?

YES /X/ NO /___/

b) Is it an effectiveness supplement? N/A

YES /___/ NO /___/

If yes, what type? (SE1, SE2, etc.) _____

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /X/ NO /___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

_____

_____

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:
This is an original NDA not a supplement.

d) Did the applicant request exclusivity?

YES /X/ NO //

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?
5 years

e) Has pediatric exclusivity been granted for this Active Moiety?

No, studies are ongoing.

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx to OTC switches should be answered NO-please indicate as such)

YES /___/ NO /X/

If yes, NDA #_____. Drug Name _____.

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /X/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /X/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /X/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

_____ _____

_____ _____

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

_____ _____

_____ _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

_____ _____

_____ _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # _____ YES /___/ ! NO /___/ Explain: _____

Investigation #2

IND # _____ YES /___/ ! NO /___/ Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ ! NO /___/ Explain _____

_____ ! _____

_____ ! _____

Investigation #2

YES /___/ Explain _____ ! NO /___/ Explain _____

_____ ! _____

_____ ! _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

Signature /S/ Date 7/26/99
Title: Regulatory Project Manager

Signature of Office/ /S/ Date 7/26/99
Division Director _____

cc: Original NDA Division File HFD-93 Mary Ann Holovac

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NDA/PLA/PMA # 21-036 Supplement # _____ Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD-530 Trade and generic names/dosage form: Relenza® (zanamivir for inhalation) Action: AP AE NA

Applicant Glaxo Wellcome Therapeutic Class 7030120 Antiviral – Anti-Influenza – Systemic.

Indication(s) previously approved: none.

Pediatric information in labeling of approved indication(s) is adequate ___ inadequate ___

Indication in this application Treatment of influenza.

___ 1. **PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

___ 2. **PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

X 3. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

___ a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.

___ b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.

___ c. The applicant has committed to doing such studies as will be required.

X (1) Studies are ongoing,

___ (2) Protocols were submitted and approved.

___ (3) Protocols were submitted and are under review.

___ (4) If no protocol has been submitted, attach memo describing status of discussions.

___ d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

___ 4. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.

___ 5. **If none of the above apply**, attach an explanation, as necessary.

ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

/S/ Regulatory Management Officer 7/15/99

Signature of Preparer and Title Date

cc: Orig NDA/PLA/PMA # 21-036
Div File
NDA/PLA Action Package
HFD-006/ SOlmstead (plus, for CDER/CBER APs and AEs, copy of action letter and labeling)

NDA 21-036

RELENZA®
(zanamivir for inhalation)

DEBARMENT CERTIFICATION

Glaxo Wellcome hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act of in connection with this application.

13 OCT 98

Charles E. Mueller
Head, US Clinical Compliance
World Wide Compliance

Date

APPEARS THIS WAY
ON ORIGINAL

Time Sensitive Patent Information

Pursuant to 21 CFR § 314.53
for

Patent Information for Relenza™ (zanamivir for inhalation)

The following is provided in accord with the Drug Price Competition and Patent Term Restoration Act of 1984:

Trade Name: Relenza™

Active Ingredient: Zanamivir

Strength: 5 milligrams of zanamivir per blister

Dosage Form: Inhalation Powder

Route of Administration: Oral Inhalation

US Patent	Expiration date	Type of Patent	Patent Owner	U.S. Agent
5,360,817	1 November, 2011	Drug Product: Composition/ formulation.	Biota Scientific Management Pty., Limited	Glaxo Wellcome Inc.
5,648,379	15 July, 2014	Drug Product: Composition/ formulation / method of use	Biota Scientific Management Pty., Limited	Glaxo Wellcome Inc.
4,627,432	9 December, 2003	DISKHALER™ inhaler device in combination with the ROTADISK™ blister pack.	Glaxo Group Limited	Glaxo Wellcome Inc.
4,778,054	18 October, 2005	ROTADISK™ blister pack..	Glaxo Group Limited	Glaxo Wellcome Inc.
4,811,731	29 July, 2006	DISKHALER™ inhaler device.	Glaxo Group Limited	Glaxo Wellcome Inc.
5,035,237	30 July, 2008	DISKHALER™ inhaler device in combination with the ROTADISK™ blister pack.	Glaxo Group Limited	Glaxo Wellcome Inc.
Des. 379,506	27 May, 2011	DISKHALER™ inhaler device.	Glaxo Group Limited	Glaxo Wellcome Inc.

The Undersigned declares that US Patent 5,360,817 covers the composition and / or formulation of Relenza ™ (zanamivir for inhalation).

The Undersigned declares that US Patent 5,648,379 covers the formulation, composition, and / or method of use of Relenza ™ (zanamivir for inhalation).

The Undersigned declares that US Patent 4,627,432 covers the delivery system of Relenza ™ (zanamivir for inhalation).

The Undersigned declares that US Patent 4,778,054 covers the delivery system of Relenza ™ (zanamivir for inhalation).

The Undersigned declares that US Patent 4,811,731 covers the delivery system of Relenza ™ (zanamivir for inhalation).

The Undersigned declares that US Patent 5,035,237 covers the delivery system of Relenza ™ (zanamivir for inhalation).

The Undersigned declares that US Patent Des. 379,506 covers the delivery system of Relenza ™ (zanamivir for inhalation).

Please address all communications to:

David J. Levy, Ph.D.
Patent Counsel
Glaxo Wellcome Inc.
Intellectual Property Department
Five Moore Drive
Research Triangle Park, NC 27709
(919) 483-7656

Respectfully submitted,

29 September 1998
Date

James P. Riek
Attorney for Applicant
Glaxo Wellcome, Inc.

#70-580 Lynbc

MAR 17 1999

NDA 21-036

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

Dear Mr. Alfors:

Please refer 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. Please additionally refer to the February 24, 1999, meeting of the Antiviral Drug Products Advisory Committee.

The following requests for information are designed to provide clarifications to the available data, additions based on data that may soon be available, or suggestions for data collection plans, that would help to address some of the issues arising from discussions to date. The objective is not to replace the primary analyses but to provide elements, including analyses that have previously been completed, in a coherent overview of the application. Please also include any additional information that addresses issues from the Advisory Committee discussion. Please be advised that additional requests may be made as the result of ongoing discussions or after receipt of the initial response.

I. Clinical issues

A. Subgroup analyses that could be done uniformly for each study:

1. The following analyses should be performed separately for studies NAIB3001, NAIA3002, NAIB3002, NAIA2005, NAIB2005, NAIB2007, and NAIA/B2008, and presented so that the results can be compared between studies[1]. We recognize that some components of these analyses have already been presented but it would be useful to see them performed using uniformly defined endpoints and subgroup definitions across all available treatment studies. For each analysis, please provide tabular and graphic frequency distributions (graphics to include histogram, Kaplan-Meier graph, or both where applicable), as well as analyses of median and mean values where applicable. Please provide p values for each analysis with an explanation of the method utilized. Each of the analyses should be presented for the total population in each study and for the following subgroup breakdowns: age (12-17, 18-49, and 50 years and over), baseline temperature (38.2 C and below, 38.3 C and above), duration of symptoms at entry (less

[1] NAIA/B2008 to be presented for North American sites, European sites, and all sites combined, in each case comparing the bid treatment group to the bid placebo group and the qid treatment group to the qid placebo group.

than 24 hours and 24 hours or more, if that is the only measurement that can be applied uniformly across studies), and baseline severity. For all analyses, please provide separate results for the intent-to-treat and influenza positive populations.

a. The first endpoint of interest remains the primary time-to-alleviation endpoint as defined in the principal phase 3 treatment studies.

b. Additional endpoints analyzed should include at least the following: time to alleviation without relief medications, time to eradication (specified symptoms scored as absent) without relief medications, time to alleviation and to eradication without subsequent rise in any principal symptom (and without any rise lasting more than one diary card entry), investigator's global assessment of patient's symptoms, and time to return to normal activities.

c. Please also analyze time course of temperature measurements, activity level, and a total symptom score (sum of scores for individual symptoms), and compare each of these between treatment groups for each day of symptom recording.

2. Please develop and present an analysis of subjects with a rise in symptoms after initial satisfaction of the alleviation criteria for each principal treatment study. Please also perform such an analysis for symptoms that occur after satisfaction of the criteria for alleviation without ongoing use of relief medications. In addition to analyses using principal symptoms, please also analyze any post-alleviation rise in secondary symptoms such as loss of appetite. These analyses should include at least the following components:

   a. Please present an analysis of the relationship of these events to treatment group (study drug assignment), demographics, and entry characteristics such as baseline severity and temperature. This should include proportion of subjects in each treatment group with any post-alleviation symptom rise, proportion of post-alleviation diary card time points containing an above-threshold symptom for each treatment group, and other applicable analyses.

   b. Please present an analysis of the time course of these events including onset relative to treatment start and stop dates, onset relative to protocol-defined time of alleviation and time of alleviation without relief medications, and onset and duration relative to use and cessation of relief medication.

   c. Please present an analysis of the specific symptoms and symptom combinations involved in these events, and their durations.

   d. Please present an analysis of subjects' reports of activity level and overall severity of disease over the time period in which any post-alleviation increases in symptom scores occur, and the relationship between symptom score reports and any decreases in activity or increases in overall severity score.

e. Please describe the impact of these analyses on interpretation of the principal primary and secondary endpoints.

3. Please consider any possible analysis that would stratify or adjust for the effect of differential use of relief medications on endpoints and treatment effect.

4. Multivariate analysis may be presented for some of the above factors as appropriate.

B. Status report of ongoing studies:

Please provide a list of all ongoing studies (including treatment and prophylaxis trials) with summary of current and planned enrollment for each.

C. Safety information in patients with underlying pulmonary disease:

1. Please provide any available information on pulmonary function tests and other safety data from the ongoing study in persons with asthma and COPD. If possible, additional assessment of PFTs should be incorporated, at least in a significant subset of subjects, to have serial spirometry at initial and final dosing (at least covering the first 1 hour post dosing - such as 5, 10, 15, 30, 60 minutes; at a minimum, consider first-dose pre-dose and 5, 10, 15, 30 minutes post-dose FEV1) to provide information such as pre- and post-dose FEV1 comparable to your existing phase 1 study. We would appreciate any additional information from this study that can be collected and would like to discuss whether sufficient information is available for a formal interim analysis. Please include a geographic breakdown (North America versus other) of any information provided from this study.

2. For the ongoing asthma/COPD study, please note the following additional suggestions:

a. Ideally diaries should track asthma medication use, particularly beta agonists/bronchodilators.

b. For tracking of exacerbations, there should be a standard definition of exacerbation.

c. A priori definitions of grades of asthma severity would be useful to facilitate exploratory analyses of subgroups.

d. Assessment of pre-existing sleep disturbance would be helpful in interpreting on-study sleep disturbance endpoints.

e. The instruction to use zanamivir after beta agonist dosing, and to measure PEFR at a time other than just after beta agonist use, increases the importance of in-clinic post-dose spirometry and must also be borne in mind for label instructions.

3. Please provide any available information on underlying disease and pulmonary function tests from the ongoing CASG study. Please provide any additional safety information available from that study including a complete report on the second death that has been reported.

4. Please provide additional information on all subjects who developed pneumonia or other lower respiratory infection during the treatment and prophylaxis studies.

D. Issues regarding elderly subjects:

1. For the North American nursing home prophylaxis study, please provide any available update information particularly regarding safety in patients with underlying medical problems.

2. As you are aware, several issues have been raised regarding the conduct of the Lithuanian study, and these will be addressed in a separate communication.

E. Other safety issues:

1. Please provide additional information on influenza negative subjects in each of the principal treatment studies. This should include comparison of duration and severity of each symptom on zanamivir versus placebo, and presentation of adverse event data. For any results that suggest a difference between treatment groups (positive or negative), please provide appropriate explanatory reasoning and analyses.

2. Please provide additional information on minority subjects in each of the principal treatment studies. This should include comparison of duration and severity of each symptom on zanamivir versus placebo, and presentation of adverse event data. Please provide any additional information available for minority populations or plans for obtaining such information.

3. Please provide a comparison of the bid and qid placebo groups in NAIA/B2008 for time to primary endpoint, time course of individual symptoms, and adverse event profile. This can serve as an introduction to discussion of whether a no-treatment control group should be added to certain future studies in addition to active drug and vehicle control.

4. Please provide any additional information available on high-risk groups. In particular, please include a breakdown of time to alleviation and complications for high-risk subjects from North American sites in NAIA2008 compared with the appropriate controls, and any information on high-risk subgroups other than the elderly and respiratory-disease subgroups addressed above. Please include a plan for providing follow-up on emergency IND recipients.

II. Virology issues

A. Please provide a summary of all results comparing quantitative recovery of virus from subjects in different treatment groups at each time point assessed for each treatment study. Please also provide a summary of all results comparing proportion of subjects with recovery of virus in different treatment groups at each time point assessed for each treatment study.

B. Please provide a proposal for quantitative and qualitative viral cultures over time in ongoing and future studies, including some late post-treatment sampling. Please consider nasal cultures for quantitative purposes in addition to throat swabs for sampling of the site of drug administration, or provide other means and rationales for maximizing the detection of virus as well as the detection of resistance. The proposal should cover both treatment and prophylaxis studies, with particular attention to subgroups such as elderly, children, and immunocompromised patients.

C. Please provide a proposal for monitoring and surveillance of resistance emergence using multiple assays, including cell-culture-based assays and in vivo assays in addition to the neuraminidase enzyme activity assay. Please consider whether a cell-culture-based assay can be developed using a cell type with sialic acid receptors similar to human receptors, and address the possibility of assessing the ability of resistant viruses to infect different cell types (e.g. from different organ system origins). Whenever possible, analysis of serial mutations over time should be included in resistance monitoring. Anti-enzyme activity should not be presented as equivalent by definition to anti-viral activity, and the enzyme activity assay should not be the sole means of screening for resistance in any study. Please also address cross-resistance issues.

D. Please provide a proposal for investigating antigenicity of mutant virus and the possibility that treatment-emergent mutations could affect antigenic drift. This proposal should include any short-term studies that can be completed and presented in the near future, as well as plans for longer-term monitoring in clinical contexts. Please consider whether any additional information can be derived from stored treatment or prophylaxis trial specimens regarding antigenic variation and antigen specificity of antibody responses, especially for any subjects who may have acquired influenza transmitted from drug-exposed subjects.

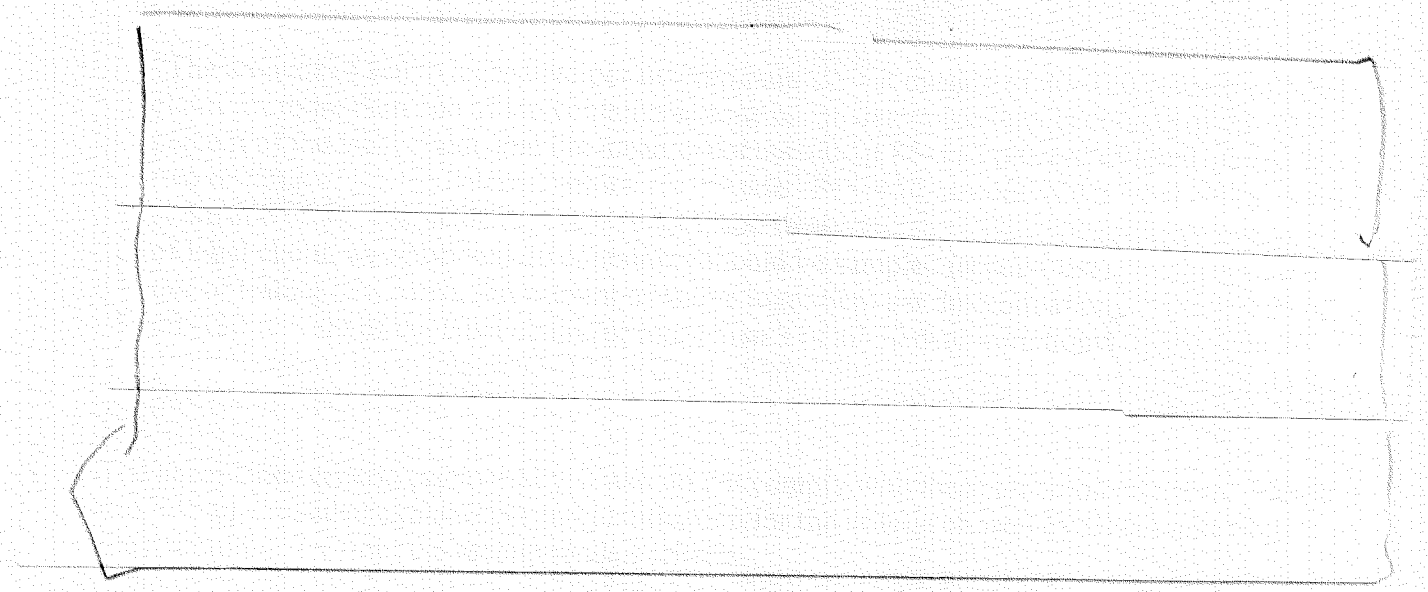
1. As an example of short-term studies that could be done to provide some reassurance regarding this issue, please consider testing influenza virus mutants that were grown in the presence of zanamivir and have changes in the hemagglutinin in parallel with the parent virus in hemagglutination inhibition tests with a panel of post-infection ferret sera made against well-characterized influenza reference strains. If HI tests show antigenic changes, neutralization tests might also be done to compare the ability of standard sera from humans or animals to neutralize the mutant and parent viruses.

2. Please provide any other information available on studies of antibody specificity in the context of zanamivir administration. Please indicate plans for further study of antibody specificity.

E. Please provide any additional information from completed prophylaxis study NAIA3005 that is not already included in the Clinical Study Report in NDA 21-036. Please submit a complete electronic dataset for this study, so that this information can be examined in the context of supportive evidence for antiviral activity. Please include any virologic results from this and other prophylaxis studies including any information on proportion of subjects with virus recovered, quantity of virus, antigenic characterization, transmission, and antibody production.

F. Please provide more information regarding the zanamivir-dependent growth mentioned in the NDA submission both in connection with in vitro passage of viral isolates under drug pressure and in connection with clinical isolates (particularly influenza B) with and without drug pressure. Please include background information regarding the concept of drug dependence in viral isolates and how this relates to analogous phenomena in clinical bacteriology; complete information on how the phenomenon of zanamivir dependence has been defined and detected; all information available on in vivo correlation; and proposed plans for monitoring of potential clinical significance.

III. Chemistry issues



IV. Use and instruction issues

A. Please develop, and submit for review, a protocol for testing of comprehension and use of the patient instructions under conditions similar to anticipated use. This should include plans for testing in an adequately varied population and iterative improvement of the instructions to address obstacles to effective use which may be identified. We will be able to provide a separate list of comments on the instructions already submitted to us.

B. Please submit for review your proposal for training of health care providers in the appropriate use of this drug/device/delivery system and in optimal approaches to patient instruction.

V. Expert reports

Please provide any available expert reports, or reports of advisory groups, from other jurisdictions where this drug is approved or under review. Please include any approval letters, package inserts, or reports of inspections which are applicable.

VI. Timeline

At your earliest convenience, please provide a timeline for response to each of the above points to facilitate timely review of your application. We will be glad to discuss or clarify any of these requests.

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

APPEARS THIS WAY
ON ORIGINAL