CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-036/S-001

ADMINISTRATIVE DOCUMENTS
CORRESPONDENCE

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.

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).

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,

15 October 1999
Date

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

cdernet
Center for Drug Evaluation and Research

DDMS

Exclusivity Summary Form

(Modified: October 14, 1998)

EXCLUSIVITY SUMMARY FOR NDA # 21-036 SUPPL # 001

Trade Name: Relenza **Generic Name:** (zanamivir for inhalation)

Applicant Name: Glaxo Wellcome, Inc. **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/___/ NO /X/

b) Is it an effectiveness supplement?

YES /X/ NO /___/

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

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:

_____

_____

GlaxoWellcome

Yoerg
Styrt
Baylor
Package

April 21, 2000

DESK COPY

Heidi M. Jolson, M.D., M.P.H., Director
Division of Antiviral Drug Products
Attn: Document Control Room
Food and Drug Administration
Fourth Floor, HFD-530
9201 Corporate Blvd.
Rockville, MD 20850

Re: NDA 21-036/S-001; RELENZA® (zanamivir for inhalation)
Response to FDA Request/Comment: Acceptance of Draft Labeling

Dear Dr. Jolson:

Reference is made to NDA 21-036/S-001 for Relenza (zanamivir for inhalation), as submitted on October 25, 1999. The purpose of this Supplemental Application was to expand the indication for Relenza to included treatment of influenza in pediatric patients. Please also refer to the fax of April 20, 2000 from Ms. Yoerg regarding revisions to the draft Package Insert, Patient Information and Patient Instructions for Use. The purpose of this letter is to provide official notification of our acceptance of all the proposed revisions and to provide 'clean copy' draft labeling to reflect the accepted revisions.

We appreciate your Review Team's efforts to bring this draft labeling to finalization. We have reviewed the proposed revisions in the faxed copy provided to us on April 20th. We have no further comments and have accepted your revisions as proposed.

This submission provides the following documents:

- Package Insert (clean copy)
- Patient Information/Patient Instructions for Use (clean copy)
- Package Insert (MS Word 'compare document', approved package insert compared to the draft package insert provided with this submission.)

Glaxo Wellcome Research and Development

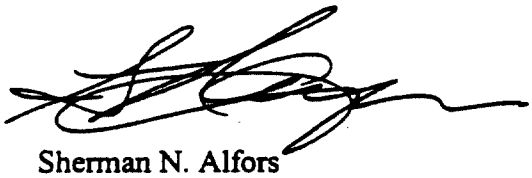
Five Moore Drive
PO Box 13398
Research Triangle Park
North Carolina 27709-3398

Telephone
919 483 2100

A Division of
Glaxo Wellcome Inc.

This letter is provided in duplicate. Four desk copies are being sent directly to Ms. Virginia Yoerg for distribution to the review team. In addition, a copy of the labeling has been sent via electronic mail to Ms. Yoerg. Please contact me at (919) 483-6030 for any matters regarding this application. Thank you.

Sincerely,



Sherman N. Alfors
Project Director
Regulatory Affairs

Attachments: 1) Revised Professional Package Insert
2) Revised Patient Information/Revised Patient Instructions for Use
3) Package Insert (MS Word 'compare document')

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338.
Expiration Date: April 30, 2000.
See OMB Statement on last page.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Glaxo Wellcome Inc.	April 21, 2000
TELEPHONE NO. (Include Area Code)	**FACSIMILE (FAX) Number *(Include Area Code)***
(919) 483-2100	(919) 483-5756

APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code and U.S. License number if previously issued)*:
Five Moore Drive
Research Triangle Park, NC 27709

AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (if previously issued): 21-036/S-001

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
zanamivir for inhalation	Relenza® (zanamivir for inhalation)

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*:
5-(acetylamino-4-[(aminoiminomethyl)-amino]-2,6-anhydro-3,4,5-trideoxy-D-glycero-D-galacto-non-2-enonic acid

CODE NAME (If any):

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Powder	5 mg	oral

(PROPOSED) INDICATION(S) FOR USE:
Treatment of influenza A and B

APPLICATION INFORMATION

APPLICATION TYPE (check one)
[X] NEW DRUG APPLICATION (21 CFR 314.50) [ ] ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314 94)
[ ] BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE [X] 505 (b) (1) [ ] 505 (b) (2) [ ] 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION (check one)
[ ] ORIGINAL APPLICATION [ ] AMENDMENT TO A PENDING APPLICATION [ ] RESUBMISSION
[ ] PRESUBMISSION [ ] ANNUAL REPORT [ ] ESTABLISHMENT DESCRIPTION SUPPLEMENT [ ] SUPAC SUPPLEMENT
[ ] EFFICACY SUPPLEMENT [ ] LABELING SUPPLEMENT [ ] CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT [X] OTHER

REASON FOR SUBMISSION:
Response to FDA Request/Comment: Acceptance of Draft Labeling

PROPOSED MARKETING STATUS (check one) [X] PRESCRIPTION PRODUCT (Rx) [ ] OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED: 1

THIS APPLICATION IS [X] PAPER [ ] PAPER AND ELECTRONIC [ ] ELECTRONIC

ESTABLISHMENT INFORMATION N/A

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current

ilical

This application contains the following items: *(Check all that apply)*		
	1. Index	
X	2. Labeling (check one)	[X] Draft Labeling [ ] Final Printed Labeling
	3. Summary (21 CFR 314.50 (c))	
	4. Chemistry section	
	A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)	
	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)	
	C. Methods Validation Package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)	
	5. Nonclinical pharmacology and toxicology section (21 CFR 314.50 (d) (2), 21 CFR 601.2)	
	6. Human pharmacokinetics and bioavailability section (21 CFR 314.50 (d) (3) , 21 CFR 601.2)	
	7. Clinical Microbiology (21 CFR 314.50 (d) (4))	
	8. Clinical data section (21 CFR 314.50 (d) (5))	
	9. Safety update report (21 CFR 314.50 (d) (5) (vi) (b) , 21 CFR 601.2)	
	10. Statistical section (21 CFR 314.50 (d) (6) , 21 CFR 601.2)	
	11. Case report tabulations (21 CFR 314.50 (f) (1) , 21 CFR 601.2)	
	12. Case reports forms (21 CFR 314.50 (f) (2) , 21 CFR 601.2)	
	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))	
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b) (2) or (j) (2) (A))	
	15. Establishment description (21 CFR Part 600, if applicable)	
	16. Debarment certification (FD&C Act 306 (k)(1))	
	17. Field copy certification (21 CFR 314.5 (K) (3))	
	18. User Fee Cover Sheet (Form FDA 3397)	
X	19. OTHER (Specify) **Response to FDA Request/Comment: Acceptance of Draft Labeling**	

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biologic product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99 and 601.12.
6. Regulations on reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
	Sherman N. Alfors **Project Director, Regulatory Affairs**	**April 21, 2000**

ADDRESS (*Street, City, State, and ZIP Code*)	Telephone Number
Five Moore Drive **Research Triangle Park, NC 27709**	**(919) 483-6030**

Public reporting burden for this collection of information is estimated to average 40 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

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Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

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DRAFT

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANTIVIRAL DRUG PRODUCTS

DATE: VERY ROUGH FIRST DRAFT April 11, 2000

TO: NDA 21-036, S-001

DRAFT

FROM: Medical Officer, HFD-530
Medical Team Leader, HFD-530

SUBJECT: Draft group leader memorandum for zanamivir pediatric efficacy supplement

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I. Introduction

In support of an indication for inhaled zanamivir dry powder for treatment of influenza in pediatric patients, the applicant has submitted safety and efficacy data from a randomized double-blind placebo-controlled study of treatment efficacy (NAI30009) that enrolled 471 children aged 5 to 12 years. Limited supporting data were submitted from a second study (NAI30010) that was principally designed to examine occurrence of secondary influenza cases within households; from this second study, safety information was submitted for children in the relevant age group who received an investigational prophylaxis regimen of zanamivir or matching placebo, and safety and efficacy information were submitted for children who were considered to be household index cases of influenza or influenza-like illness and who received the proposed marketed treatment regimen of zanamivir or matching placebo.

The principal safety and efficacy issues in the review of this supplement are well summarized by Dr. Melisse Baylor in the primary clinical review. This memorandum will focus on some of the principal issues related to these studies, their context from previous studies of influenza treatment in children, and other concurrent events related to use of zanamivir that were taken into consideration in the review process.

II. Efficacy issues

The principal pediatric efficacy study, NAI30009, used a primary endpoint and efficacy population comparable to those used in other recent studies of drugs for influenza. Improvement was measured as the time (in half-days) until fever was absent and other predefined major

symptoms were recorded as absent/minimal (or no more than mild in the case of cough), with symptoms maintained below this threshold for a further 24 hours (thus, three recordings at half-day intervals). Subjects with at least one laboratory test confirming influenza virus infection (influenza positive) were pre-defined as the primary population for analysis of efficacy. Several pre-defined principal secondary endpoints and sensitivity analyses were examined for consistency with the primary analysis.

A. Magnitude of effect and comparison with other zanamivir studies

The principal analyses of primary and major secondary endpoints were generally compatible with a median time to reach the improvement threshold that was about a day earlier in the zanamivir group than the placebo group. The actual point estimate for the primary analysis was 1.25 days, but on examination of this and other analyses it appeared most appropriate to include this in the general category of "about a day" together with other analyses yielding a point estimate of 1.0 days (see additional discussion in the Medical Officer and Statistical reviews, and below). Although the magnitude of effect was thus modest, the primary analysis was highly statistically significant ($p<.001$) and numerous secondary analyses yielded similar comparisons between zanamivir and placebo groups with p values low enough to be highly suggestive of a genuine (but small) difference between treatment groups. The magnitude of treatment effect was within the range observed for previous zanamivir studies and within the range considered to be clinically meaningful in pre-study discussions based upon experience with other drugs for influenza.

Among the endpoints showing comparable treatment effects in the influenza-positive population were time to alleviation as defined for the primary analysis and as re-assessed censoring records with incomplete data and no definite evidence of reaching the primary endpoint; time to alleviation without ongoing use of standardized relief medications; and time to return to normal activities. Analysis of all randomized subjects (including those not confirmed to have influenza) yielded smaller differences between treatment groups but again favored the zanamivir group with a p value less than .05.

Several issues in the interpretation of on-treatment and post-treatment data required further examination. The investigators' assessment of illness severity at day 3 showed no appreciable difference between the zanamivir and the placebo group; however, severity scores were higher in the zanamivir group than the placebo group at baseline, so a shift to more equal distribution at day 3 was compatible with (though not definitive of) greater improvement on zanamivir. A higher proportion of zanamivir subjects than placebo subjects had present/moderate symptoms recorded lasting more than one-half day after reaching the primary alleviation endpoint; however, there was no excess in the zanamivir group when any post-endpoint symptom rise (regardless of duration) was counted, and the zanamivir group continued to show earlier resolution than the placebo group when the alleviation definition was restricted to exclude any subject with a subsequent symptom rise in either of these categories. The means of parental assessments of disease severity showed an advantage in the zanamivir group that was maintained throughout the

symptom recording period and a monotonic pattern of improvement; although this assessment should not be given undue weight because of problems in interpreting a ranked-categorical variable analyzed as an ordinal variable (expressed as a percentage of the total if all determinations were "severe" and then as a mean of individual determinations), it is useful as supporting information to combine with other analyses in forming an overall picture of the progress of each treatment group. Measures of viral shedding showed no appreciable difference between treatment groups but also did not suggest viral rebound on the day 6 measurements, although the apparent insensitivity of the culture methods (leading to low yields even in the placebo group, and therefore small numbers of positive results for comparisons either between treatment groups or between time points) limit the interpretation of this finding.

A sizable minority of subjects in this study were infected with influenza B, and this subgroup showed a substantial treatment effect. In combination with results from other zanamivir studies that included influenza B as well as influenza A infections, these results do not permit any definite conclusion about whether the drug has a greater effect in influenza B or in influenza A, but are highly suggestive that there is some effect in both influenza A and influenza B.

The much smaller amount of information available from pediatric index cases in NAI30010 provided support for a difference between zanamivir and placebo groups in time to symptom improvement. Although not originally proposed in support of treatment efficacy and not considered as a pivotal study in itself, this study yielded results compatible with the results of the central pediatric efficacy study.

B. Appropriate description and representation

Because of the inherently subjective nature of symptom-determined endpoints, and because of the inherently approximate and variable nature of influenza symptom durations, differences between groups may be difficult to detect but still more difficult to describe quantitatively when detected. There is room for debate as to whether small fractions of a day contain clinically useful information in such descriptions. In the analysis of NAI30009, the primary analysis point estimate of 1.25 days' difference between groups was not robust to further analyses as described in the Medical Officer Review and the Statistical Review. The median time to alleviation of 5.25 days in the placebo group was considered to be an artifact of the equal number of subjects with times of 5.0 and below or 5.5 and above, such that omitting one subject could change this median by 0.25 days (a fairly large fraction of the modest estimated treatment difference). Furthermore, this estimate was very sensitive to the treatment of missing values: subjects who stopped recording symptoms before completing the entire study period, and had not reached the predefined primary endpoint when they stopped recording symptoms, were assigned the longest possible time to alleviation and therefore contributed to a longer median than if some of those subjects had had more complete data and earlier alleviation. Inspection of the missing values indicated that there were very few missing values in the zanamivir group and re-allocation or censoring of those observations would generally yield the same median (4.0 days) as the primary analysis; however, for the placebo group, there were more missing values and censored

observations, or any additional data showing early alleviation for even one of the subjects with missing data, or use of other common methods for allocation of subjects with missing results, would likely result in a median of 5.0 days (and therefore a difference of 1.0 days between treatment groups). A number of important secondary analyses, as well as the difference between means of the two treatment groups, likewise clustered in the area of a one-day treatment difference. After careful review of the primary and principal secondary analyses and sensitivity analyses, and extensive discussion among clinical and statistical reviewers, the consensus was that the primary analysis appropriately suggested the existence of a treatment effect but that adding a quarter-day that would be canceled by the removal or re-assignment of a single subject had no clear clinical meaning and was potentially misleading in the context of all available data. Therefore, to the extent that it is possible and important to quantitate the benefit of zanamivir in this study, about a day of difference in average outcomes appeared to most appropriate description.

C. Age, ethnicity, high-risk medical condition, and country effects

Several subgroup analyses (of the numerous analyses described in the reviews) required particularly close attention. These were considered in terms of their potential impact on approval, on labeling, and on phase 4 commitments.

Several different age breakdowns within NAI30009 were examined. Estimates of treatment effect were more variable in magnitude as smaller subgroups were examined. In general, the youngest age groups tended to have somewhat smaller point estimates of treatment effect than the overall study population. There was not a statistically significant treatment-by-age interaction and there was not a linear relationship between age and treatment effect (in fact, the oldest children in the study, whose ages approached or overlapped those included in previous adult/adolescent studies, also had lower point estimates than 7, 8, 9, and 10 year olds). Thus, there was not a single definitive age cutoff for efficacy based solely on the results of this study. However, the suggestion of lower efficacy in the youngest children than in the overall population was reinforced by similar findings in NAI30010, although again there were variable results as smaller subgroups were examined. Furthermore, the small single-dose pharmacokinetic study, in which inspiratory flow rates through the Diskhaler device were measured, suggested substantial problems with use of the device by the youngest children in this first-use acute setting (see further discussion below). After extensive examination of the data and discussion among clinical. biopharmaceutics, and statistics reviewers, it was concluded that the data did not provide adequate support at this time for use of this therapy by 5 and 6 year old children.

The treatment effect measured in both NAI30009 and NAI30010 appeared largely attributable to subjects classified by the applicant as Caucasian or White, who constituted the vast majority of study subjects. When influenza positive subjects were examined within each of the racial/ethnic categories used in the study reports, no clear demonstration of lack of efficacy or of detriment was observed, but numbers were too small to draw any firm conclusions. Previous zanamivir studies also had shown variable results in nonmajority subjects and insufficient data to confirm

or refute a treatment effect compatible with that observed in majority subjects. A phase 4 commitment was proposed to obtain safety and efficacy data in a more representative population.

Few subjects with high-risk medical conditions were included in this supplement. In NAI30009, the small number of enrollees with underlying respiratory or cardiac disease (presumably mostly asthma) showed a treatment effect with zanamivir, but this was not reproduced in the even smaller number of such subjects in NAI30010. Furthermore, there was concern about adverse events (discussed further below) although these were not described as serious. Overall, the high-risk data did not provide sufficient evidence of benefit to cancel out the statements already in the package insert that safety and efficacy have not been demonstrated in persons with high-risk medical conditions, and the strengthening of cautionary language discussed below.

As noted in previous zanamivir studies, NAI30009 showed somewhat less treatment effect in the U.S. sites than in non-U.S. sites, and in North American sites than in non-North American sites. This difference was not duplicated in NAI30010, where the number of non-U.S. subjects was extremely small. As discussed in the Statistical review (and again, as in prior zanamivir studies), use of standardized relief medications appeared to be substantially higher in the U.S. [need to check with Jonathan's review, can't keep track of US vs NA analyses], in both the zanamivir and the placebo groups, and it is plausible that this could be a partial explanation: if aggressive use of symptom relief medication actually diminishes symptoms, the marginal add-on effect of zanamivir might be less impressive than in settings where little symptomatic relief medication is used. There was not a similar relationship between use of relief medication and zanamivir treatment effect within U.S. sites, but this comparison is not necessarily analogous: it could be proposed, for example, that patients who do not use symptom relief medication in a cultural setting conducive to such use are mostly those with symptoms so mild that no need for symptom relief is perceived, and therefore with such mild self-resolving disease that there is little margin for showing a treatment effect of any intervention.

D. Context of other anti-influenza drugs

The historical background for evaluation of anti-influenza drugs in pediatric patients is scanty. Rimantadine is approved for prophylaxis in children but not for treatment of established influenza; there are two published studies [references]. One study found no difference between rimantadine and acetaminophen in symptoms; the other showed an early decrease in symptom scores and viral shedding on rimantadine, but both the symptom scores and viral shedding rose again in the rimantadine group after the first few days and by day – were actually higher on rimantadine than on acetaminophen. Amantadine is approved both for prophylaxis and for treatment in children; review material suggests that the basis of the treatment approval was the inclusion of studies that enrolled both adults and children, with duration of fever as the principal outcome measure.

III. Safety issues

Consideration of the adverse event reports for the studies in the pediatric supplement is well outlined in Dr. Baylor's review. Other safety issues arising from the original NDA for zanamivir, which were felt to require additional attention during the time period covered by this review, are also briefly summarized below.

A. Safety in pediatric studies

As outlined in Dr. Baylor's review, there was little difference between adverse event profiles of zanamivir and placebo in the pediatric treatment studies submitted. Although lactose powder inhalants have been studied and approved in other settings without raising major safety issues, the possibility that some local irritative effects may be produced by the lactose vehicle cannot be excluded on the basis of a comparison between active drug (with lactose vehicle) and placebo (consisting of the lactose vehicle), and it is important that this issue be addressed in the package insert; however, potentially relevant adverse events were reported only by very small percentages of the subjects in treatment studies. The one serious adverse event reported with hospitalization involved a patient who reportedly had a bacterial infection concomitantly with influenza A; this reinforces another point made in a recent FDA Public Health Advisory (discussed further below) and in proposed labeling changes, that a diagnosis of influenza and institution of antiviral therapy do not obviate the possibility of bacterial infection requiring other treatment.

Although investigational regimens of zanamivir for prophylaxis have not yet been reviewed for efficacy, safety data were requested for children in the age group covered by this pediatric efficacy supplement who received such a prophylactic regimen in a recently completed study (NAI30010 contact subjects). Overall reporting of adverse events was higher in subjects who did not have influenza-like symptoms at enrollment and received either zanamivir or placebo than in subjects who received treatment-dose zanamivir or placebo and had influenza-like symptoms as a condition of starting treatment. Differences could be partly because events compatible with the usual expected course of influenza would be reported as study symptoms rather than adverse events in treatment subjects; and partly because any intercurrent respiratory infections (such as common colds) circulating during the winter-season study, as well as incidental symptoms such as headaches that are common in the general population, would be reported as adverse events for prophylaxis subjects and would be recorded over a longer medication use period than for treatment-regimen exposure. However, there did appear to be an excess of some upper respiratory symptoms in zanamivir recipients. In addition, the small number of pediatric subjects with underlying respiratory disease who received prophylaxis-dose were all reported to have some adverse event coded as lower-respiratory-tract; when more information on lower respiratory tract events was requested, most of these were reported as "influenza-like symptoms" without further elaboration. Although adverse events on the prophylaxis regimen were described by the applicant as neither serious nor treatment-limiting and not clearly drug related, it was considered important to provide relevant information in the package insert.

B. Other safety issues

During review of the original NDA, concerns were raised about the possibility of bronchospasm occurring in patients with underlying airways disease, and whether zanamivir might add to the potential for exacerbations that could occur with influenza itself. These concerns, and the lack of demonstrated efficacy in patients with underlying high-risk medical conditions and/or complicated influenza, were reflected in the initial package insert. However, during initial post-marketing experience, a number of reports were received of deterioration of respiratory function in patients receiving zanamivir; while causality was generally difficult to assess in the uncontrolled setting and in the presence of concomitant disease, a number of these events occurred in patients who were described as having severe or poorly decompensated pulmonary disease. In addition, a number of reports were received in which patients presenting with "flu-like" symptoms were started on zanamivir without antibacterial treatment and proved to have bacterial sepsis either producing influenza-like prodromal symptoms or developing as a complication of an initial influenza-like illness. Because of these reports, an FDA Public Health Advisory was issued on January 12, 2000, to reinforce the importance of evaluating and treating concomitant bacterial infection and the level of caution that should be exercised if zanamivir was prescribed for patients with underlying respiratory disease. Recommendations were made to the applicant for revised labeling to strengthen these cautionary messages.

It was considered important that the revised cautionary labeling, under ongoing discussion with the applicant during review of the pediatric efficacy supplement, be implemented no later than the action on the supplement such that strong cautionary language should accompany any label that would include pediatric efficacy data. It was further considered important that recommendations already made to the applicant for a pregnancy category C designation be implemented. Additional revisions to safety labeling were proposed on the basis of postmarketing reports which provided experience from a broader range of patient exposures, although with less complete information for each report and less opportunity to assess potential causality, than was possible for clinical trial populations. In the course of the review process, the applicant was also asked to provide for a patient package insert providing appropriate safety and efficacy information (in addition to the instructions and warnings previously packaged with the drug), and for a Dear Health Professional letter alerting prescribers to the safety-related labeling changes. Ongoing enhanced monitoring was requested as a phase 4 commitment.

IV. Viral resistance

Assessment of the potential for emergence of resistance to zanamivir continues to be hampered by the limited assay methods in use (including lack of a well established cell-culture-based assay) and low yield from culture specimens. The applicant was asked to address these issues in phase 4 commitments, and to add cross-resistance information to the package insert.

V. Device/delivery system use and instruction

Systematic studies of device use and potential for improvement of instructions have been requested as phase 4 commitments both for the original NDA and for the current supplement. In the course of review of the current supplement, the applicant provided more detailed information from their single-dose pharmacokinetic study, in which a small number of children were asked to inhale through the Diskhaler device and peak inspiratory flow was measured. This study enrolled no five-year-olds; of two six-year-olds, one did not provide a measurable inhalation on request and no inhalation data were available for the other; of two seven-year-olds, one did not provide a measurable inhalation on request and the other produced two inhalations with peak flow below the 60 L/min proposed by the applicant as likely to provide delivery of drug from the device. Older children had variable measurements but did not as uniformly suggest inadequate device use. No information is available to define quantitative relationships between inspiratory flow (or serum levels, also low or unmeasurable in the youngest children using the Diskhaler) and clinical efficacy, and the number of children in this study could not be assumed to provide adequate representation of the target age group. However, the combination of age-stratified results from the efficacy studies and the small amount of inhalation data available was of concern with regard to likely device use and efficacy in the youngest children. After close examination of the data from all available studies and discussion among clinical, biopharmaceutics, chemistry, and statistics reviewers, the conclusion was that insufficient data were available to support zanamivir treatment for five and six year olds at this time; that ability of young children to use the device should be carefully evaluated if the drug is prescribed for them; and that these conclusions should be reflected in the package insert, with phase 4 commitments to improve the information base.

VI. Summary

Efficacy results from the principal pediatric treatment study (NAI30009) supported a modest shortening of time to symptom improvement in children receiving zanamivir compared with placebo. Results from pediatric index cases in NAI30010 (family transmission study) were compatible with this finding. The principal safety concerns were those raised by the original adults studies and reinforced by postmarketing experience, most prominently the risk of decreased respiratory function in patients with underlying respiratory disease, as well as the risk of untreated concomitant bacterial infection addressed in the January Public Health Advisory. Co-ordinated examination of the efficacy and pharmacokinetic studies suggested that the demonstration of efficacy was more solidly based in the population ages seven years and up, and was not sufficient at this time in younger children.

VII. Conclusions

The conclusion of co-ordinated review and internal discussions was that sufficient information had been submitted to support approval of dry powder inhaled zanamivir for treatment of uncomplicated acute illness due to influenza A and B in patients ages seven years and older, with appropriate warnings and precautionary language regarding risks of adverse events, particularly respiratory adverse events in patients with underlying respiratory disease.

_____
Barbara A. Styrt, M.D., M.P.H.
Medical Officer, DAVDP

_____
Stanka Kukich, M.D.
Medical Team Leader, DAVDP

Concurrence:
HFD-530/Dir/HJolson

cc:
HFD-530/NDA21036
HFD-530/Division File
HFD-530/Dir/HJolson
HFD-340
HFD-530/Chem/Boring
HFD-530/Pharm/Wu
HFD-530/Biopharm/Suarez
HFD-530/Micro/Battula
HFD-530/Stat/Aras
HFD-530/MTL/SKukich
HFD-530/MO/BStyrt
HFD-530/CSO/Yoerg

c:\data\NDA21036\glm01

Form OGD-011347 Revised 8/27/97
cc: Original NDA Division File HFD-93 Mary Ann Holovac

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?

Three

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

YES /___/ NO /X/

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 /X/ NO /___/

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

NDA# 21-036 Relenza (zanamivir for inhalation) 5 mg powder

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 /X/ 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 /X/ 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 /X/

(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 /X/

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:

NAI 30009

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 /X/

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 /X/

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"):

① NAI 30009 "A Double-Blind, Randomized, Placebo-Controlled, Parallel-Group Multicenter Study to Investigate the Safety & Efficacy of Zanamivir (GG167) 10 mg Administered Twice Daily for 5 Days in the Treatment of Symptomatic Influenza A and B Viral Infections in Children Ages 5-12."

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 # 51,672 _____

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 /X/

If yes, explain: _____

_____

Signature: /S/ ***Date:*** 4/5/00
Title: Regulatory Project Manager

Signature of Office/Division Director

Signature: /S/ ***Date:*** 4/26/00

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

Prev Page

VI. Marketing Exclusivity

NDA 21-036

RELENZA ® (zanamivir for inhalation)
Supplemental New Drug Application for the
Treatment of Influenza A and B in Pediatric Patients

Request for Marketing Exclusivity

Under sections 505(c)(3)(D)(iv) and 505(j)(5)(D)(iv) of the Federal Food, Drug, and Cosmetic Act, and section 314.108(b)(5) of Title 21 of the Code of Federal Regulations, Glaxo Wellcome Inc. requests 3 years of exclusivity from the date of approval of zanamivir (inhaled dry powder, Rotadisk®), for the treatment of influenza A and B in children ages 5-12.

Glaxo Wellcome Inc. requests this determination of exclusivity because this new drug application contains the following "new" investigation which was conducted and sponsored by Glaxo Wellcome and which is essential to the approval of the application. This investigation is "essential to the approval of the application" in that the application could not be approved by FDA without the following investigation:

> **NAI30009:** A Double-Blind, Randomized, Placebo-Controlled, Parallel-Group Multicenter Study to Investigate the Efficacy and Safety of Zanamivir (GG167) 10mg Administered Twice Daily for 5 Days in the Treatment of Symptomatic Influenza A and B Viral Infections in Children Ages 5-12

This clinical investigation is "new" in that it has not been relied on by FDA to demonstrate substantial evidence of effectiveness of a previously approved drug product for any indication or of safety for a new patient population and does not duplicate the results of any such investigations.

This investigation was "conducted or sponsored by Glaxo Wellcome" in that Glaxo Wellcome was the sponsor of the investigational new drug applications [redacted] under which the investigation took place.

Update of Pediatric Exclusivity

On September 22, 1998, Glaxo Wellcome provided the Division of Antiviral Drug Products with a Proposed Pediatric Study Request ([redacted] Number 097), in order to seek a Written Request in accordance with Section 505A of the Federal Food, Drug and Cosmetic Act. On December 29, 1998, the Office of Drug Evaluation IV provided Glaxo Wellcome with an official pediatric Written Request [redacted] NDA 21-036).

The Written Request identified four types of studies that would provide information sufficient to qualify under Section 505A. The studies are briefly summarized as:

Study 1 – Phase 3 study to evaluate the treatment of inhaled dry powder zanamivir as determined by effects of time to alleviation of influenza symptoms in pediatric patients from 5 to 12 years of age.

Study 2 – Phase 3 study to evaluate the prophylactic efficacy of inhaled dry powder zanamivir as determined by effects on transmission of symptomatic influenza within families with at least one member in the age range from 5 to 17 years.

Study 3 – Phase 3 study to evaluate the treatment efficacy of inhaled dry powder zanamivir as determined by effects on time to alleviation of influenza symptoms in adolescent patients diagnosed with underlying respiratory disease, in the age range of 12 to 17.

Study 4 – Study to assess the ability of children and adolescents of various ages to use the zanamivir dry powder inhalation system based on patient and parental use of package instructions.

The Phase 3 clinical study submitted with this supplement (NAI30009) fulfills the request outlined in "Study 1."

This information is provided for update purposes only. The clinical study referenced above is not being submitted as a complete response to the Pediatric Written Request, and we are not asking for a determination regarding pediatric exclusivity at this time.

MESSAGE CONFIRMATION

05/01/00 09:18
ID=DAVDP

DATE	S.R-TIME	DISTANT STATION ID	MODE	PAGES	RESULT	
05/01	03'37"	913015946463	CALLING	09	OK	0000

05/01/00 09:13 DAVDP → 913015946463 NO.953 D01

DIVISION OF ANTIVIRAL DRUG PRODUCTS

Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-530
Rockville, MD 20850

FACSIMILE TRANSMISSION COVER SHEET

Date: 5/1/00 Number of Pages (including cover sheet): 9

To: Mary Ann Holovac

Company: FDA

Fax Number: 301 594 6463

Message: Per your request. Date of approval of

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	21036	**Trade Name:**	RELENZA (ZANAMIVIR) INHALATION 5 MG POWD
Supplement Number:	1	**Generic Name:**	ZANAMIVIR
Supplement Type:	SE1	**Dosage Form:**	Powder; Inhalation
Regulatory Action:	AP	**Proposed Indication:**	Treatment of influenza A and B in pediatric patients.

ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?

YES, Pediatric data exists for at least one proposed indication which supports pediatric approval

What are the INTENDED Pediatric Age Groups for this submission?

____NeoNates (0-30 Days)
____Infants (1-24 Months)
____Children (25 Months-12 years)
____Adolescents (13-16 Years)
_X_ Other Age Groups (listed): 7 years and older

Label Adequacy	Adequate for SOME pediatric age groups
Formulation Status	NO NEW FORMULATION is needed
Studies Needed	No further STUDIES are needed
Study Status	

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? YES

COMMENTS:
See Phase 4 commitments detailed in the supplemental NDA 21-036 approval letter dated April 26, 2000.

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, VIRGINIA YOERG

Signature /S/ Date April 25, 2000

Supplemental New Drug Application

NDA 21-036; Relenza® (zanamivir for inhalation)
Treatment of Influenza A and B in Pediatric Patients

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 in connection with this application.

	14 OCT 95
Charles E. Mueller Head, Clinical Compliance World Wide Compliance	Date

Attachment C: Form Memo for Requesting Clinical Inspections

MEMORANDUM

Date: December 9, 1999

To: Antoine El-Hage, GCPB Reviewer/HFD-47

Through (optional): David LePay, Director, DSI/HFD-45

From: Virginia L. Yoerg, DAVDP, PM/HFD-530

Subject: Request for Clinical Inspections
NDA 21-036/Supplement No: SE1-001
Glaxo Wellcome, Inc.
Relenza® (zanamivir for inhalation) for pediatrics ages 5-11

Section A: Protocol/Site Identification

As discussed with you, the following protocols/sites essential for approval have been identified for inspection. These sites are listed in order of priority. This Supplement provides for a new indication and expansion of the patient population (pediatric).

We chose the two sites with the most patients (both for protocol NAI30009):

Dr. James Hedrick - 45 patients
Kentucky Pediatric Research / Adult Unit
201 South 5th St.- Suite 3
Bardstown, KY 40004

Dr. Gerald Bottenfield -21 patients
R/D Clinical Research Inc
135 Oyster Creek Drive- Suite W
Lake Jackson, TX 77566

We have requested inspections because (please check appropriate statements):

___ There are insufficient domestic data; or

___ Only foreign data are submitted to support an application; or

___ Domestic and foreign data show conflicting results pertinent to decision-making; or

___ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations.

_✓_ Other: This is a pediatric supplement for a drug for which pediatric study sites have not previously been inspected. We need inspections for this reason and because of variability in previous adult study results.

Section D: Goal Date for Completion

We request that the inspections be performed and the Inspection Summary Results be provided by February 25, 2000. We intend to issue an action letter on this application by **February 25, 1999**. However, the PDUFA date is **April 26, 2000**.

Should you require any additional information, please contact Virginia Yoerg, Regulatory Project Manager at (301) 827-2419 or write to yoergv@cder.fda.gov (e-mail).

concurrence:
HFD-530/MTL/Kukich SK 12/13/99
HFD-530/MO/Styrt RSS 12/10/99
HFD-530/MO/Baylor MSB 12/13/99
HFD-530/RPM/Yoerg 12/9/99

Distribution: NDA 21-036/S-001
HFD-530/Division File
HFD-530/Yoerg
HFD-47/El-Hage
HFD-45/Program Management Staff

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: February 3, 2000

FROM: Antoine El-Hage, Ph.D., Branch Chief
Good Clinical Practice II, HFD-47
Division of Scientific Investigations

SUBJECT: Clinical Inspection Summary - **NDA 21-036 (supplement #SE-001)**

TO: Virginia L. Yoerg, PM
Melissa Baylor, M.D.
Division of Antiviral Drug Products (HFD-530)

APPLICANT: Glaxo Wellcome, Inc.

DRUG: Relenza (zanamivir for inhalation) for Pediatrics ages 5-12; inhaled dry powder

CHEMICAL CLASSIFICATION: 6P

THERAPEUTIC CLASSIFICATION: Priority (4 months)

INDICATION: Anti-influenza

CONSULTATION DATE: December 9, 1999

DIVISION ACTION GOAL DATE: April 26, 2000

ACTION GOAL DATE: February 25, 2000

I. BACKGROUND

Relenza (zanamivir) is an antiviral drug that was approved on July 26, 1999, for treatment of influenza. This supplement is under review for a new indication and expansion of patient population to pediatric patients ages 5-12. Zanamivir is the first in a class of drugs designed to inhibit influenza A and B virus neuraminidase while sparing mammalian neuraminidase. Neuraminidase acts by facilitating the release and spread of new viruses by removing sialic acid from the complex carbohydrates located on the cell surface and on virus particles. Other agents to date are approved only for treatment of influenza A. Viral resistances to currently approved agents develop rapidly. One pivotal trial used in the NDA submitted by Glaxo Wellcome for Relenza is protocol NAI 30009. These two sites were identified as essential for approval and were chosen because of variability of results in previous studies and large enrollees.

II. RESULTS

	City	State	IN	Assigned	Action	Reviewer	Class
J. Hedrick	Lake Jackson	KY	DA	12/10/00	2/1/00	AEH	NAI
G. Bottenfield	Bardstown	TX	DA	12/10/00	2/2/00	AEH	NAI

A. Dr. Hedrick:

This site enrolled forty-five (45) subjects; one dropout. Ten (10) subjects' files were reviewed and appeared to be well organized, documented and no problems found. Data generated from this site appear to be acceptable.

B. Dr. Bottenfield:

This site enrolled twenty-one (21) subjects; twenty (20) subjects completed and one subject withdrew due to personal reasons. Ten (10) subjects' files were reviewed. No problems noted. All events were accurately reported. Data are acceptable.

Limitation of the inspections – none
No follow-up actions are planned.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

The two requested inspections have been completed. No objectionable conditions were found which would preclude use of the data submitted in support of the pending application (supplement).

Key to Classifications
NAI = No deviation from regulations. Data acceptable
VAI = Minor deviations(s) from regulations. Data acceptable
VAIr= Deviation(s) form regulations, response requested. Data acceptable
OAI = Significant deviations for regulations. Data unreliable
Pending = Inspection not completed

/S/
Antoine El-Hage, Ph.D.
Branch Chief
Good Clinical Practice II, HFD-47

cc:
NDA #21-036
HFD-45
HFD-47/KMS
HFD-47/AEH
HFD-47/rf/cf
HFD-45/rf

1-007/1550

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANTIVIRAL DRUG PRODUCTS

DATE: February 1, 2000

TO: [redacted] erial no. 083)

FROM: Medical Officer, HFD-530

SUBJECT: Annual report for IND [redacted], zanamivir aqueous solution

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The principal new information in this annual report concerns study report WD1999/00225/01, Three times daily subcutaneous embryofetal development study in the Wistar Han rat (Study no. R22558). This study report was submitted and reviewed as serial no. 082. Pharmacology/Toxicology staff have recommended revisions to the pregnancy information in the package insert for Relenza (NDA 21-036) based on the results suggesting some delay in skeletal development. These recommendations have been conveyed to the sponsor and discussion of appropriate language for label changes is in progress

/S/

Barbara A. Styrt, M.D., M.P.H.
Medical Officer, DAVDP

Concurrence:
HFD-530/MTL/SKukich SK 2/2/00

cc:

[redacted]
HFD-530/Division File
HFD-530/Dir/HJolson
HFD-530/Pharm/Wu
HFD-530/MTL/SKukich
HFD-530/MO/BStyrt
HFD-530/CSO/Yoerg

yoerg - 330

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: February 29, 2000

To: Sherman N. Alfors

Address: Glaxo Wellcome Inc.
Five Moore Drive
Research Triangle Park, NC 27709

From: Virginia L. Yoerg, Regulatory Project Manager, HFD-530 vly 2/29/00

Through: Stanka Kukich, M.D., Medical Team Leader, HFD-530 SK 2/29/00
Barbara Styrt, M.D., M.P.H., Medical Reviewer, HFD-530 BS 2/29/00
Melisse Baylor, M.D., Medical Reviewer, HFD-530 MSB 2/29/00
James Farrelly, Ph.D., Pharmacology/Toxicology Team Leader, HFD-530 JF 2/29/00
Kuei-Meng Wu, Ph.D., Pharmacology/Toxicology Reviewer, HFD-530 KMW 2/29/00

IND/NDA: [redacted] NDA 21-036

Subject: Relenza label: Pregnancy Category

The following labeling comments are in response to your serial submission 082, dated October 13, 1999, serial submission 0085, dated February 9, 2000, and serial submission 0086, dated February 22, 2000 to IND [redacted]. These submissions were presented to the Reproductive Toxicology Committee on February 25, 2000. The Committee determined that a Pregnancy Category C designation was appropriate to be placed into the RELENZA label under the "Pregnancy" section. Below is proposed wording to be added to the "Pregnancy" section immediately after the first paragraph. At the beginning of the Pregnancy section, the pregnancy category should be changed from B to C.

[redacted]

We are providing this in addition to the safety labeling and pediatric labeling comments faxed on Friday, February 25, 2000 in the effort to expedite labeling discussions related to the pediatric efficacy

supplement. We look forward to your early response addressing all of these communications, and additional comments may follow as needed.

We are providing the above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me if you have any questions regarding the contents of this transmission.

/S/

Virginia L. Young
Regulatory Project Manager
Division of Antiviral Drug Products

DAVDP/HFD-530 • 5600 Fishers Lane • Rockville, MD 20857 • (301) 827-2335 • Fax: (301) 827-2523

cc:
Original NDA 21-036
Division File
HFD-530/MOTL/Kukich
HFD-530/MO/Styrt
HFD-530/MO/Baylor
HFD-530/PharmToxTL/Farrelly
HFD-530/PharmTox/Wu
HFD-530/RPM/Yoerg

NDA 21-036

Facsimile

C:\ [redacted]

DIVISION OF ANTIVIRAL DRUG PRODUCTS

Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-530
Rockville, MD 20850

FACSIMILE TRANSMISSION COVER SHEET

Date: 2/29/00 Number of Pages (including cover sheet): 3

To: Sherman Albers

Company: Glaxo Wellcome

Fax Number: 919 483 5756

Message: Label revisions regarding pregnancy category. Will send e-copy via e-mail.

From: VIRGINIA YOERG

Title: Reg. PM

Telephone: 301 827 2335 Fax Number: 301 827 2471
or 2523

MESSAGE CONFIRMATION

02/29/00 10:49
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DATE	[illegible]	DISTANT STATION ID	MODE	PAGES	RESULT	
02/29	[illegible]	919 990 5756	CALLING	03	OK	0000

02/29/00 10:4[illegible] [illegible] 34835756 NO.759 P01

DIVISION OF ANTIVIRAL DRUG PRODUCTS

Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-530
Rockville, MD 20850

FACSIMILE TRANSMISSION COVER SHEET

Date: 2/29/00 Number of Pages (including cover sheet): 3

To: Sherman Albers

Company: Glaxo Wellcome

Fax Number: 919 483 5756

Message: Label revisions regarding

MAR 16 2000

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANTIVIRAL DRUG PRODUCTS

MEMORANDUM

DATE: March 16, 2000
TO:
FROM: Medical Officer, HFD-530
SUBJECT: Reproductive toxicology study; follow-up on zanamivir pregnancy labeling

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This one-volume submission contains the sponsor's response to an FDA request to change the pregnancy category in the Relenza labeling from B to C on the basis of Pharmacology/Toxicology review of a recently submitted reproductive toxicology study distinct from those included in the original NDA. The sponsor proposed that pregnancy category B would be appropriate on the basis of their re-evaluation of the study data. This submission was discussed with the Pharmacology/Toxicology review team who reviewed the sponsor's response and presented the data to the Reproductive Toxicology Committee. The conclusion was that pregnancy category C would be appropriate, and this information was conveyed to the sponsor, who indicated in a teleconference of March 1, 2000, that the package insert would be revised to indicate pregnancy category C. The sponsor has also been asked to plan a Dear Health Professional communication that would address this change together with safety-related labeling changes based on postmarketing experience.

/S/
Barbara A. Styrt, M.D., M.P.H.
Medical Officer, DAVDP

Concurrence:
HFD-530/MTL/SKukich SK 3/16/00

cc:
HFD-530/
HFD-530/Division File
HFD-530/Dir/HJolson
HFD-340
HFD-530/Pharm/Wu
HFD-530/Biopharm/Reynolds
HFD-530/MTL/SKukich
HFD-530/MO/BStyrt
HFD-530/CSO/Yoerg

FINANCIAL DISLCOSURE AS TO CLINICAL INVESTIGATORS

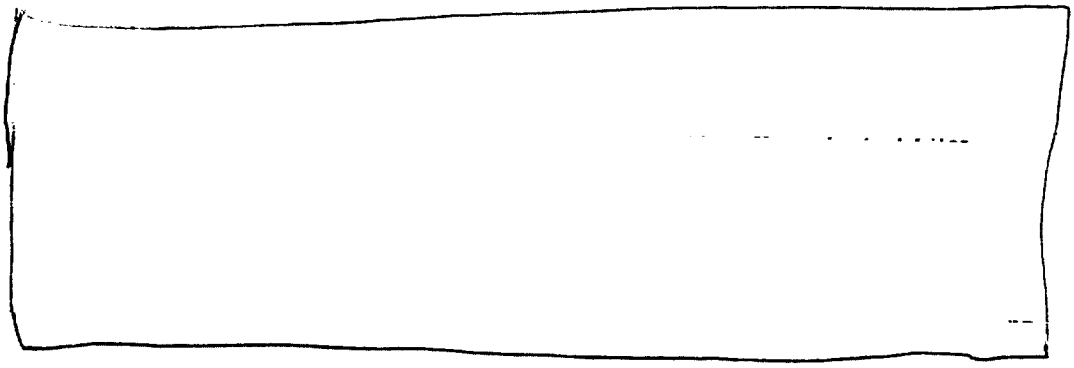
RELENZA® (zanamivir for inhalation)

NDA 21-036; Supplemental New Drug Application for the Treatment of Influenza A and B in Pediatric Patients

In compliance with the Final Rule on Financial Disclosure by Clinical Investigators published on February 2, 1998 (63 *FR* 5233), as subsequently revised by publication on December 31, 1998 (63 *FR* 72171) (hereafter collectively referred to as the "rule"), financial interest information is provided for clinical investigators participating in studies covered by the rule included in New Drug Application 21-036, Supplement for Pediatric Use for Relenza (zanamivir for inhalation) for the treatment of influenza A and B in pediatric patients. The following synopsis includes a description of methods used for the collection and reporting of the investigator financial disclosure information. Form FDA 3454 (Certification: Financial Interests and Arrangements of Clinical Investigators) and supporting tables and Form FDA 3455 (Disclosure: Financial Interests and Arrangements of Clinical Investigators) and supporting information can be found in this section.

The following is the "covered clinical studies" for purposes of the rule for which Glaxo Wellcome was the sponsor:

PROTOCOL NO.	PROTOCOL TITLE	STUDY START DATE	STOP DATE
NAI30009	A DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED, PARALLEL-GROUP MULTICENTER STUDY TO INVESTIGATE THE EFFICACY AND SAFETY OF ZANAMIVIR (GG167) 10 MG ADMINISTERED BY INHALATION TWICE DAILY FOR FIVE DAYS IN THE TREATMENT OF SYMPTOMATIC INFLUENZA A AND B VIRAL INFECTIONS IN CHILDREN AGES 5-12	15 OCT 98	30 APRIL 99



- **Significant equity interest in the sponsor of the covered study product (21 CFR 54.4(a)(3)(iv), 54.2(b))**

Relying on information obtained from the clinical investigators, Glaxo Wellcome has determined that one clinical investigator participating in Protocol NAI30009 has

[redacted]

information is located in this section.

Please note that information as to equity interest could not be obtained by written or verbal communications for 10 subinvestigators at two sites in the US, who did not comply with Glaxo Wellcome's request to provide equity information in a timely fashion to allow for inclusion in this submission, and one subinvestigator in Israel who could not be located. Specific information is located in this section.

In conclusion, Glaxo Wellcome does not believe [redacted] biased the outcome of Protocol NAI30009 since they each contributed only two patients to the study and the protocol was conducted as a multicenter, randomized, double, placebo-controlled trial.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0297
Expiration Date: 04-30-01

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form.

1. APPLICANT'S NAME AND ADDRESS

Glaxo Wellcome Inc.
Five Moore Drive
Research Triangle Park, NC 27709

2. TELEPHONE NUMBER *(Include Area Code)*

(919) 483-2100

3. PRODUCT NAME

Relenza® (zanamivir for inhalation)

4. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? **No**
IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW:

☐ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO _____
(APPLICATION NO. CONTAINING THE DATA).

5. USER FEE I.D. NUMBER

6. LICENSE NUMBER / NDA NUMBER

NDA 21-036

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE **EXCLUSIONS**? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92
(Self Explanatory)

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE.
(See item 7, reverse side before checking box.)

☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act
(See item 7, reverse side before checking box.)

☒ THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, drug, and Cosmetic Act
(See item 7, reverse side before checking box.)

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY
(Self Explanatory)

FOR BIOLOGICAL PRODUCTS ONLY

☐ WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION

☐ A CRUDE ALLERGENIC EXTRACT PRODUCT

☐ AN APPLICATION FOR A BIOLOGICAL PRODUCT FOR FURTHER MANUFACTURING USE ONLY

☐ AN "IN VITRO" DIAGNOSTIC BIOLOGICAL PRODUCT LICENSED UNDER SECTION 351 OF THE PHS ACT

☐ BOVINE BLOOD PRODUCT FOR TOPICAL APPLICATION LICENSED BEFORE 9/1/92

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? ☐ YES ☒ NO
(See reverse side if answered YES)

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment.

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0297)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Please **DO NOT RETURN** this form to this address.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
Sherman N. Alfors	**Project Director, Regulatory Affairs**	**October 25, 1999**

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

Form Approved: OMB No. 0910-0396
Expiration Date: 3/31/02

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

☒ (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CRF 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		
	NDA 21-036, Supplemental New Drug Application for the Treatment of Influenza A and B in Pediatric Patients	See Attached Listing

☐ (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

☒ (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
Adrian Hennah	Chief Financial Officer
FIRM / ORGANIZATION	
Glaxo Wellcome Inc.	
SIGNATURE	DATE
By G Marshall for Adrian Hennah	Oct 13, 1999

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

List of Principal and Sub-Investigators

Study #	Protocol Title
NAI30009	A Double-Blind, Randomized , Placebo-Controlled, Parallel-Group Multicenter Study to Investigate the Efficacy and Safety of Zanamivir (GG167) 10mg Administered by Inhalation Twice A Day for Five Days in the Treatment of Symptomatic Influenza A and B Viral Infections in Children Ages 5-12
Study Start Date: November 12, 1996	Study Stop Date: August 26, 1997
Study Sponsor: Glaxo Wellcome, Inc. 5 Moore Drive Research Triangle Park, NC 27709	

Principal Investigator #	Principal Investigator Indicate last name, first name	Sub-investigator(s) Indicate last name, first name
54499	Dr. Michel Accardi 304 avenue Thiers 33000 Bordeaux France	None
33349	Dr. Philippe Angeli 145 rue de Chevilly 98400 Villejuif France	None
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49759	Frederick W. Henderson, M.D. NC Children & Adults Clinical Research Foundation 109 Conner Drive, Ste 107-B Chapel Hill, NC 27514 USA	Gregory Alan Fisher, M.D. Kathleen E. Salter, M.D. Lynne R. Morgan, M.D.
12587	Kelly J. Henrickson, M.D. Medical College of Wisconsin Department of Pediatrics 8701 Watertown Plank Road Milwaukee, WI 53226-0509 USA	None

11668	Dan C. Henry, M.D. Foothill Family Clinic 2295 Foothill Drive Salt Lake City, UT 84109 USA	Amy D. Echelberger, M.D. Amy M. Geroso, M.D. Bryan L. Nelson, M.D. Cyril Bruce Callister, PAC Deborah Gobelman Donna M. Thompson Gerald Gilbert Kelty, PAC Jack A. Taylor, M.D. Jamie P. Longe, M.D. John Edward Witbeck, M.D. Joseph M. Food, PAC Konrad P. Kotardy, M.D. Shane G. Christensen, MD Sharon A. Strong, M.D. Stephen D. Coleman, M.D Stephen D. Wood, M.D. Susan B. Edwards, M.D. Timothy L. Pefaur, PAC Wesley J. Lewis, M.D.
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50497	Dr. med. Detlef Kahle Hoppestrasse 32 13409 Berlin Germany	None
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12734	Kevin R. Murphy, M.D. Midwest Allergy & Asthma Clinic, Inc. 8552 Cass Street Omaha, NE 68114 USA	George A. Zieg, M.D. Jeffrey S. Nelson, M.D. M. Ross Thomas, M.D. Thomas C. Nilsson, M.D.

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24766	David H. Ricker, M.D. Pediatrics Northwest 316 Martin Luther King, Jr. Way Tacoma, WA 98406 USA	Anne M. Pettinger, ARNP Cynthia t. Kertesz, M.D. Daniel J. Niebrugge, M.D. Gary C. Tart, M.D. Georga A. Tanbara, M.D. George W. Rurik , M.D. Jeffrey M. Jacobs, M.D. John Dimant, M.D. John F. Clapper, M.D. Karen M. Holdner, M.D. Katherine E. Brendt, ARNP Kirk N. Starr, M.D. Laura C. Macbeth, M.D. Lawrence A. Larson, DO Lori H. McDonald, M.D. Martin A. Goldsmith, M.D. Mary Ann Woodruff, M.D. Michelle E. Acker, ARNP Pamela L. LaBore, M.D. Richard F. Ory, M.D. Tara Diane Garcia, MS Tracy Ann Lin, ARNP William J. Thomas, M.D.
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53664	Thomas D. Selva, M.D. Green Meadows Pediatrics 3217 S. Providence Road Columbia, MO 12 USA	None
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43337	Dr. Georg Kurt G. von Pilgrim Elbestrasse 90 55122 Mainz Germany	None
11478	C. Ron Williams, M.D. Doctors' Clinic 2300 Fifth Avenue Vero Beach, FL 32960 USA	Adriana R. Gioia, M.D. Donald B. Morris, M.D. James J. Marino, M.D. Karen Westberry, M.D. Michael B. Wein, M.D. Patricia W. Mercer, M.D. Timothy L. Cocks, M.D.
41004	Dr. med. Christof Wittermann Muenchener Strasse 35A 82362 Weilheim Germany	None
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62822	Philippe Yaeche 10 rue Benoit Malon 76300 Sotteville les Rouen France	None
12332	Dick E. Zoutman, M.D. Kingston General Hospital 76 Stuart Street Kingston, Ontario L1H 1B9 Canada	None

List of Principal and Sub-Investigators

Listing Supporting Item (3) of Form FDA 3454

NAI30009	A Double-Blind, Randomized , Placebo-Controlled, Parallel-Group Multicenter Study to Investigate the Efficacy and Safety of Zanamivir (GG167) 10mg Administered by Inhalation Twice A Day for Five Days in the Treatment of Symptomatic Influenza A and B Viral Infections in Children Ages 5-12
Study Start Date: October 15, 1998	Study Stop Date: April 30, 1999
Study Sponsor: Glaxo Wellcome, Inc. 5 Moore Drive Research Triangle Park, NC 27709	

13347	63198 63189 63191 63213 63206 63200 63204 63202 63209	Alan R. Alexander, M.D. Daniel A. Kramer, M.D. Deborah M. Ghazoul, M.D. Harry Nudelman, M.D. Howard S. Jacobs, M.D. Jeffrey E. Lazarus, M.D. Nancy J. Lisch, M.D. P. Cooper White, M.D. Theresa M. Kammerman, M.D.	Investigator refusal to comply with request for information
33549	63780	Natalie Shilo	Investigator could not be located
24766	60881	Mary Ann Woodruff, M.D.	Investigator information not received by Glaxo Wellcome

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF INTERNAL MEETING

Date of Meeting: November 29, 1999

sNDA: NDA 21-036/S-001

Drug: Relenza® (zanamivir for inhalation)

Applicant: Glaxo Wellcome, Inc. (GW)

Indication: Treatment of Influenza A and B for ages 5-11

Participants:
Heidi Jolson, M.D., M.P.H., Division Director
Debra Birnkrant, M.D., Deputy Director
Stanka Kukich, M.D., Medical Team Leader
Melisse Baylor, M.D., Medical Reviewer
Barbara Styrt, M.D., M.P.H., Medical Reviewer
Daniel Boring, Ph.D., Chemistry Reviewer
Kellie Reynolds, Pharm.D., Biopharmaceutics Team Leader
Sandra Suarez, Ph.D., Biopharmaceutics Reviewer
Kuei-Meng Wu, Ph.D., Pharmacology/Toxicology Reviewer
Narayana Battula, Ph.D., Microbiology Reviewer
Girish Aras, Ph.D., Acting Statistics Team Leader
Z. Jonathan Ma, Ph.D., Statistical Reviewer
Anthony DeCicco, R.Ph., Chief, Project Management Staff
Virginia Yoerg, Regulatory Project Manager

Type of Meeting: Filing Meeting

Related Documents:

Background: Glaxo Wellcome, Inc. submitted this supplemental NDA on October 26, 1999. This sNDA is exempt from user fees (pediatric population). It has a 60-day filing date of December 26, 1999, and an internal goal date of February 25, 2000 (the PDUFA date is April 26, 2000). The NDA for Relenza was approved on July 26, 1999. This supplemental application is for zanamivir (powder for inhalation, 5 mg per blister), 10 mg inhaled twice daily for five days, for the treatment of influenza A and B in pediatric patients ages 5-11 years. This meeting was held to determine whether the application is filable.

Discussion

1. Chemistry

Dr. Boring stated that there are no filing issues, as the applicant cross-referenced this supplemental NDA to the original NDA (NDA 21-036).

2. Pharmacology/Toxicology

Dr. Wu concluded that there are no filing issues, as the applicant cross-referenced this supplemental NDA to the original NDA. Dr. Wu did discuss the new information from the applicant that resulted in a FDA request that the pregnancy category be changed from B to C.

3. Microbiology

Dr. Battula stated that there are no filing issues. A number of Microbiology comments will be sent to the applicant including a request for GW to sequence the entire hemagglutinin gene for resistance-associated mutations, a request that GW analyze more patient samples for genotypic and phenotypic resistance, and that GW send in the resistance data that has been completed for patients enrolled in NAI 30009. It will be important for the applicant to submit wording appropriate for a cross resistance section in the label.

4. Biopharmaceutics/Clinical Pharmacokinetics

Dr. Suarez concluded that there are no filing issues. Dr. Suarez stated that we may consider requesting several additional studies from GW in the future; such studies would include a mass balance study, a food effect study, a study to determine the exact site of action of zanamivir, and studies examining the mechanism of its renal clearance. In addition, Dr. Suarez feels that the number of patients studied in NAIA1009 was small and that better knowledge concerning the pharmacokinetics of zanamivir in children would be derived from the study of a larger number of patients.

5. Statistics

Dr. Ma stated that there are no filing issues, but FDA will request that the applicant submit a subgroup analysis based on patient age.

6. Clinical

Dr. Baylor concluded that there are no filing issues, and therefore the application is filable. FDA will request that the applicant submit more detailed efficacy data on the index patients in study NAI30010, because the submission refers to such data as supportive of efficacy although it was not proposed as supportive in the pre-sNDA discussions. There was discussion of the patient instructions and it was concluded the applicant should be asked to provide a proposal to revise these to incorporate the proposed pediatric uses.

7. Division of Scientific Investigations

Dr. Antoine El-Hage will be asked to inspect the larger U.S. sites. An official request will be completed as soon as possible.

8. Pediatric Exclusivity

Virginia Yoerg noted that this submission is not a complete response to the Pediatric Written Request issued to GW on December 29, 1998. In the submission, the applicant acknowledged that it is not a complete response to the Written Request but proposed that it would fulfill one of the four study requests toward satisfying the Written Request for pediatric exclusivity.

Conclusions

- The review team concluded that sNDA 21-036/S-001 is filable, and is designated as a priority review (six month clock) because it is the first application with efficacy information for treatment of both influenza A and influenza B in children

Action Items

- A Division of Scientific Investigations (DSI) inspection will be requested.
- Additional information will be requested from the applicant as outlined by the Microbiology, Statistical, and Clinical reviewers.
- Virginia Yoerg will review the financial disclosure information.
- The applicant will be asked to provide their timeline for a labeling supplement for timely incorporation of the pregnancy category changes recently requested by the Division.

Addendum: A list of requests for additional Microbiology information, additional Clinical/Statistical analyses, and responses to prior Pharmacology/Toxicology comments was transmitted to the applicant via telephone facsimile on **December 6, 1999.**

NDA 21-036/S-001
concurrence:
HFD-530/MQTL/Kukich SK 1/10/00
HFD-530/MO/Baylor MSB 1/11/00
HFD-530/MO/Styrt BAS 1/10/00
HFD-530/ChemTL/Miller SM 1/11/00
HFD-530/Chem/Boring ajb 1/11/00
HFD-530/BiopharmTL/Reynolds KSR 1/11/00
HFD-530/Biopharm/Suarez SS 1/12/00
HFD-530/PharmToxTL/Farrelly [illegible] 1/14/00
HFD-530/PharmTox/Wu [illegible] 1/12/00
HFD-530/StatsTL/Aras GA 1/12/00
HFD-530/Stats/Ma S.M. 1/12/00
HFD-530/MicroTL/Iacono-Connors [illegible] 1-11-00
HFD-530/Micro/Battula NB 1/12/00
HFD-530/RPM/Yoerg-12/10/99
Draft completed: Yoerg- 12/2/99

distribution:
HFD-530/NDA 21-036/S-001
HFD-530/Division File
HFD-530/MO/Wu
HFD-530/Chem/Boring
HFD-530/Biopham/Suarez
HFD-530/PharmTox/Wu
HFD-530/Stats/Ma
HFD-530/Micro/Battula
HFD-530/RPM/Yoerg

Filing Meeting

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-036/S-001

NOV 9 1999

Glaxo Wellcome Inc.
Five Moore Drive
Research Triangle Park, NC 27709

Attention: Sherman N. Alfors
Project Director, Regulatory Affairs

Dear Mr. Alfors:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: Relenza® (zanamivir for inhalation)

NDA Number: 21-036

Supplement Number: S-001

Date of Supplement: October 25, 1999

Date of Receipt: October 26, 1999

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on December 25, 1999 in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

Food and Drug Administration
Division of Anti-Viral Drug Products, HFD-530
Office of Drug Evaluation IV
Center for Drug Evaluation and Research
Attention: Document Control Room
5600 Fishers Lane
Rockville, MD 20857

Sincerely,

/S/

Anthony W. DeCicco
Supervisory Consumer Safety Officer
Division of Anti-Viral Drug Products, HFD-530
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

cc:
Original NDA 21-036/S-001
HFD-530/Div. Files
HFD-530/CSO/Yoerg

SUPPLEMENT ACKNOWLEDGEMENT

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: December 6, 1999

To: Sherman N. Alfors, Project Director, Regulatory Affairs

Address: Glaxo Wellcome Inc.
Five Moore Drive
Research Triangle Park, NC 27709

From: Virginia L. Yoerg, Regulatory Project Manager, HFD-530 VLY 12/6/99

Through: Stanka Kukich, M.D., Medical Team Leader, HFD-530 SK 12/6/99
Melisse Baylor, M.D., Medical Reviewer, HFD-530 for MB 12/6/99
Barbara Styrt, M.D., M.P.H., Medical Reviewer, HFD-530 BS 12/6/99
Kellie Reynolds, Pharm.D., Biopharmaceutics Team Leader, HFD-530 KSR 12/6/99
Sandra Suarez, Ph.D., Biopharmaceutics Reviewer, HFD-530 ESO 12/06/99
Girish Aras, Ph.D., Statistics Acting Team Leader, HFD-530 GA 12/6/99
Z. Jonathan Ma, Ph.D., Statistical Reviewer, HFD-530 GA 12/6/99 for JM
Lauren Iacono-Connors, Ph.D., Microbiology Team Leader, HFD-530 LM for LC 12/6/99
Nara Battula, Ph.D., Microbiology Reviewer, HFD-530 NB 12/6/99
Jim Farrelly, Ph.D., Pharm/Tox Team Leader, HFD-530 ESO 12/06/99
K.M. Wu, Ph.D., Pharm/Tox Reviewer, HFD-530 ESO 12/06/99

sNDA: 21-036/S-001

Subject: Requests for information regarding Supplemental NDA 21-036/S-001

The following are initial requests for information to facilitate the review of your Supplemental New Drug Application (sNDA) for the use of Relenza® for the treatment of influenza A and B in pediatric patients ages 5 through 11 years.

1. Please provide your timeline for submission of a labeling supplement to incorporate pregnancy labeling changes (refer to our fax dated November 24, 1999).

2. Please provide a proposal for revision of the printed patient instructions.

3. Please provide an analysis of safety and efficacy data from study NAI30009 by age. We suggest both the analysis of patients by year of age and the analysis of two age groups, 5 through 7 year olds and 8 through 12 year olds.

4. Please provide a table of primary outcomes by site for the U.S. sites in study NAI30009.

5. Although the results of NAI30010 have been submitted primarily for safety information, the efficacy results of the index cases in this clinical trial were also mentioned in the sNDA as supporting evidence of the efficacy of Relenza in pediatric patients. Please provide complete pediatric efficacy results from index cases in NAI30010, including an analysis of results by age subgroups comparable to those analyzed for NAI30009.

6. Please ensure that this information from NAI30010 is included in the datasets submitted electronically, including the programs needed to generate the principal efficacy outcomes.

7. The sNDA submission states that the sequencing studies of viral isolates from pediatric patients enrolled in NAI30009 are underway. Please provide your timeline for completion and for submission of these studies as well as any analysis of isolates from NAI30010. Please indicate your proposal for providing cross-resistance information and for sequencing additional areas of the hemaglutinin gene.

8. Please provide an update on the progress of juvenile inhalation studies and immunotoxicologic studies, which were agreed to as a part of GlaxoWellcome's Phase 4 commitments for the original NDA 21-036.

9. Please provide a description of the actions to be taken in order to increase the reproducibility and efficiency of pulmonary delivery to pediatric patients.

These comments are provided for your convenience as early as possible in the review process to facilitate ongoing dialog. Additional comments and requests may follow during the review.

We are providing the above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me if you have any questions regarding the contents of this transmission.

/S/

Virginia L. Yoerg
Regulatory Project Manager
Division of Antiviral Drug Products

cc:
Original NDA 21-036/S-001
Division File
HFD-530/RPM/Yoerg-12/06/99

NDA 21-036/S-001

Facsimile

Yoerg

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: **January 19, 2000**

To: **Sherman N. Alfors, Project Director, Regulatory Affairs**

Address: **Glaxo Wellcome Inc.**
Five Moore Drive
Research Triangle Park, NC 27709

From: **Virginia L. Yoerg, Regulatory Project Manager, HFD-530**

Through: **Stanka Kukich, M.D., Medical Team Leader, HFD-530** SK 1/19/00
Melisse Baylor, M.D., Medical Reviewer, HFD-530 ESO 01/19/00
Barbara Styrt, M.D., M.P.H., Medical Reviewer, HFD-530 BS 1/19/00

sNDA: **21-036/S-001**

Subject: **Requests for information and labeling comments**

The following are requests for information to facilitate the review of your Supplemental New Drug Application (sNDA) for the use of Relenza® for the treatment of influenza A and B in pediatric patients ages 5 through 11 years.

We are including our preliminary comments on the proposed changes to the Relenza® package circular. As we continue our review, additional comments may follow. We have included the proposed change in Pregnancy Category wording. This correspondence is not intended to address changes in the Precautions and other safety wording that the Division has recently discussed with you and that should also be in progress.

Please provide the data on which the table of adverse events (Table 2) in pediatric patients is based. The sNDA submission contains combined safety data from both study subjects in NAI30009 and the index cases of study NAI30010, while the proposed data in the label includes only the subjects in NAI30009. Please provide the detailed data on which the proposed label changes are based.

In addition to these labeling comments, we need several other items of information in order to review this supplement efficiently and effectively:

1. P-values for the baseline characteristics (Tables 7 through 11) of the study population in NAI30009 and for influenza A and B subgroup analysis.

2. Efficacy data for the subjects with high-risk medical conditions, especially those with high-risk respiratory conditions.

3. A more detailed description of the adverse events called viral respiratory infections and viral ENT infections in both study NAI30009 and NAI30010. Please provide individual patient data in a line listing format.

4. Diary cards for study subjects in NAI30009 and index cases in NAI30010 who were noncompliant with study drug, who went off study or off study drug prematurely, for whom consent was withdrawn, and who were on the treatment arm and experienced an adverse event.

5. Individual study subject data for the "Time from Onset of Symptoms" to the first dose of Relenza. Please provide this data in an electronic format.

Please provide a response within two weeks from the date of facsimile receipt.

We are providing the above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me if you have any questions regarding the contents of this transmission.

/S/

Virginia L. Yoerg
Regulatory Project Manager
Division of Antiviral Drug Products

cc:
Original NDA 21-036/S-001
Division File
HFD-530/RPM/Yoerg-01/19/00

NDA 21-036/S-001

Facsimile

MESSAGE CONFIRMATION

01/19/00 15:54
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DATE	S.R-TIME	DISTANT STATION ID	MODE	PAGES	RESULT	
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Division of Antiviral Drug Products (DAVDP)
Office of Drug Evaluation IV
Center for Drug Evaluation and Research
Food and Drug Administration

TELEFACSIMILE TRANSMISSION RECORD

To: Sherman N. Alfors, Project Director, Regulatory Affairs

Fax Number: (919) 483-5756

Date: January 19, 2000

Company: Glaxo Wellcome Inc.

No. of pages (excluding cover): 13

Message: Comments regarding NDA 21-036/S-001

YOERG

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: February 7, 2000

To: Sherman N. Alfors, Project Director, Regulatory Affairs

Address: Glaxo Wellcome Inc.
Five Moore Drive
Research Triangle Park, NC 27709

From: Virginia L. Yoerg, Regulatory Project Manager, HFD-530

Through: Stanka Kukich, M.D., Medical Team Leader, HFD-530 SK 2/7/00
Melisse Baylor, M.D., Medical Reviewer, HFD-530 MSB 2/7/00
Barbara Styrt, M.D., M.P.H., Medical Reviewer, HFD-530 2/7/00 BRS

sNDA: 21-036/S-001

Subject: Request for reevaluation of table in January 14, 2000 submission

Please refer to your Supplemental New Drug Application (sNDA) for the use of Relenza® for the treatment of influenza A and B in pediatric patients ages 5 through 11 years.

Your submission dated January 14, 2000 contains data analyzing the results of NAI30009 by age group. Please reevaluate the "Difference in Days" for the table on page 10 (under Section 5.2) and its source table (Table 13).

We are providing the above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me if you have any questions regarding the contents of this transmission.

/S/

Virginia L. Yoerg
Regulatory Project Manager
Division of Antiviral Drug Products

cc:
Original NDA 21-036/S-001
Division File
HFD-530/RPM/Yoerg-02/07/00
HFD-530/MO/Baylor
NDA 21-036/S-001

Facsimile

MESSAGE CONFIRMATION

02/07/00 16:44
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DATE	S.P-TIME	DISTANT STATION ID	MODE	PAGES	RESULT	
02/07	16:43	919 990 5756	CALLING	02	OK	0000

02/07/00 16:4[illegible] [illegible] - 919194835756 NO.679 P01

Division of Antiviral Drug Products (DAVDP)
Office of Drug Evaluation IV
Center for Drug Evaluation and Research
Food and Drug Administration

TELEFACSIMILE TRANSMISSION RECORD

To: Shermar N. Alfors, Project Director, Regulatory Affairs

Fax Number: (919) 483-5756

Date: February 07, 2000

Company: Glaxo Wellcome Inc.

No. of pages (excluding cover): 1

Message: Clinical request regarding NDA 21-036/S001

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

HHD-530
Yoerg

FEB 7 2000

Gerald W. Bottenfield, M.D.
R/D Clinical Research, Inc.
135 Oyster Creek Drive, Suite W
Lake Jackson, Texas 77566

Dear Dr. Bottenfield:

Between January 10 and 12, 2000, Ms. Constance M. Harris, representing the Food and Drug Administration (FDA), met with you and your staff to review your conduct of a clinical study (protocol #NAI 30009) of the investigational drug Relenza (zanamivir), performed for Glaxo Wellcome, Inc. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

From our evaluation of the inspection report and the documents submitted with that report, we conclude that you did adhere to all pertinent federal regulations and/or good clinical investigational practices governing your conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown Investigator Harris during the inspection. Should you have any questions or concerns about any aspect of the clinical testing of investigational drugs, please contact me at (301)594-1032.

Sincerely yours,

/S/

Antoine El-Hage, Ph.D.
Branch Chief
Good Clinical Practice II, HFD-47
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place
Rockville, MD 20855

CFN: 3001665807
Field Classification: NAI
Headquarters Classification:
__X__1)NAI
_____2)VAI-no response required
_____3)VAI-response requested

If Headquarters classification is a different classification, explain why:

cc:
HFA-224
HFD-132
HFC-230
HFD-530 Review Div. Dir.
HFD-530 MO (Baylor)
HFD-530 PM (Yoerg)
HFD-530 Doc. Rm. NDA #20-136
HFD-47 r/f
HFD-47 c/r/s GCP file #9956
HFD-47 (AEH/KS)
HFR-SW150 DIB (Thornburg)
HFR-SW1540 BIMO Monitor (Martinez)
HFR-SW1540 Field Investigator (Harris)
r/d:(AEH):(1/31/2000)
reviewed:AEH:(date)
f/t:mb:(date)

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Note to Rev. Div. M.O.

This site enrolled twenty-one subjects; twenty completed the study and one subject withdrew due to personal reasons. Ten (10) subjects' files were reviewed - no problems noted. All events were accurately recorded and reported. Data are acceptable.