

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-500

Administrative Documents

ITEM 13 AND ITEM 14

PATENT INFORMATION

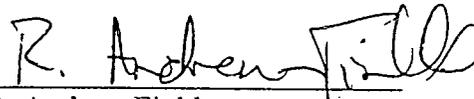
In accordance with 21CFR314.53, Triangle Pharmaceuticals, Inc. submits the following patent information in support of the Original New Drug Application for COVIRACIL® (emtricitabine) Capsules and Oral Solution.

Patent No.	Expiry Date	Type of Patent	Owner
5,210,085	May 11, 2010	Method of Use	Emory University
5,814,639	September 29, 2015	Composition	Emory University
5,914,331	September 29, 2015	Composition	Emory University

The undersigned declares that Patents 5,210,085; 5,814,639; 5,914,331:

- i. have been licensed to Triangle Pharmaceuticals, Inc.;
- ii. cover the formulation, composition and method of use of Coviracil; and
- iii. Coviracil is the product that is the subject of this application for which approval is sought.

Signed:



R. Andrew Finkle

Executive Vice President, Secretary and General Counsel

EXCLUSIVITY SUMMARY for NDA # 21-500 SUPPL # _____

Trade Name Emtriva Generic Name emtricitabine

Applicant Name Gilead Sciences, Inc. HFD-530

Approval Date July 2, 2003

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 questions about the submission.

- a) Is it an original NDA? YES/✓/ NO /___/
- b) Is it an effectiveness supplement? YES /___/ NO /___/

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

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

YES /✓/ 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:

d) Did the applicant request exclusivity?

YES // NO /___/

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

Five years.

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

YES /___/ NO //

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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 //

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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

YES /___/ NO //

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

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

YES /___/ NO /✓/

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

NDA # _____

NDA # _____

NDA # _____

2. Combination product. Not applicable.

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 /___/

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 9. IF "YES," GO TO PART III.

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

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

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

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

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

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

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

YES /___/ NO /___/

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

YES /___/ NO /___/

If yes, explain: _____

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

YES /___/ NO /___/

If yes, explain: _____

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

Investigation #1, Study # _____

Investigation #2, Study # _____

Investigation #3, Study # _____

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

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

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 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:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

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

Investigation #1 YES /___/ NO /___/
Investigation #2 YES /___/ NO /___/
Investigation #3 YES /___/ NO /___/

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

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

- (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"):

Investigation #__, Study # _____
Investigation #__, Study # _____
Investigation #__, Study # _____

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

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

Investigation #1	!	
IND # _____	!	YES /___/
	!	NO /___/ Explain: _____
	!	_____
	!	_____
Investigation #2	!	
IND # _____	!	YES /___/
	!	NO /___/ Explain: _____
	!	_____
	!	_____

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

Investigation #1	!	
YES /___/ Explain _____	!	NO /___/ Explain _____
_____	!	_____
_____	!	_____
Investigation #2	!	
YES /___/ Explain _____	!	NO /___/ Explain _____
_____	!	_____
_____	!	_____

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

YES /___/ NO /___/

If yes, explain: _____

6/24/03

Signature of Preparer
Title: Regulatory Health Project Manager

Date

15/

7/02/03

Signature of Office or Division Director

Date

cc:
Archival NDA
HFD-530/Division File
HFD-530/RPM/Yoerg
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

NDA/BLA #: 21-500 Supplement Type (e.g. SE5): _____ Supplement Number: _____

Stamp Date: September 3, 2002 Action Date: July 2, 2003

HFD-530 Trade and generic names/dosage form: Emtriva (emtricitabine) 200 mg capsules

Applicant: Gilead Sciences, Inc. Therapeutic Class: Antiretroviral

Indication(s) previously approved: None.

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application: 1

Indication #1: Treatment of HIV-1 infection in combination with other antiretroviral agents in adults

Is there a full waiver for this indication (check one)?

Yes: Please proceed to Section A.

No: Please check all that apply: Partial Waiver Deferred Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____	kg _____	mo. _____	yr. _____	Tanner Stage _____
Max _____	kg _____	mo. _____	yr. _____	Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg _____ mo. _____ yr. birth Tanner Stage _____
Max _____ kg _____ mo. _____ yr. 16 Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
 - Disease/condition does not exist in children
 - Too few children with disease to study
 - There are safety concerns
 - Adult studies ready for approval
 - Formulation needed
- Other: Pediatric studies are ongoing.

Date studies are due (mm/dd/yy): 12/31/03, as stated in the March 2, 2001 amended Written Request.

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg _____ mo. _____ yr. 6 Tanner Stage _____
Max _____ kg _____ mo. _____ yr. 18 Tanner Stage _____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Health Project Manager

cc: NDA

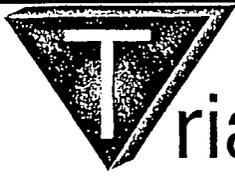
HFD-950/ Terrie Crescenzi
HFD-960/ Grace Carmouze
(revised 9-24-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
301-594-7337

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Virginia Yoerg
7/2/03 12:27:36 PM



Triangle Pharmaceuticals

Anne F. McKay
Vice President, Drug Regulatory Affairs

August 29, 2002

DEBARMENT CERTIFICATION

In support of the New Drug Applications for Coviracil® (emtricitabine) Capsules (NDA 21-500) and Covriacil® Oral Solution (NDA 21-499), and in accordance with the Generic Drug Enforcement Act of 1992, Triangle Pharmaceuticals, Inc., certifies that it did not and will not use, in any capacity, the services of any person (including a company or partnership), debarred under subsections (a) or (b) [Section 306(a) or (b)] of the Food, Drug, and Cosmetic Act.

Anne McKay

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: <http://www.fda.gov/cder/pdufa/default.htm>

1. APPLICANT'S NAME AND ADDRESS
Triangle Pharmaceuticals, Inc.
4611 University Drive
4 University Place
Durham, NC 27707

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER
NDA 021-500

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?
 YES 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: see below

2. TELEPHONE NUMBER (Include Area Code)
(919) 493-5980

(APPLICATION NO. CONTAINING THE DATA).

3. PRODUCT NAME
Coviracil (emtricitabine) Capsules

6. USER FEE I.D. NUMBER
N/A

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 COMMERCIALY (Self Explanatory)

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

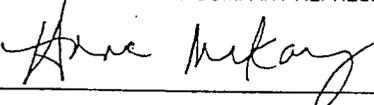
Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments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

Department of Health and Human Services
Food and Drug Administration
CDER, HFD-94
1401 Rockville Pike
Rockville, MD 20852-1448

and

Food and Drug Administration
CDER, HFD-94
12420 Parklawn Drive, Room 3046
Rockville, MD 20852

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.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE


TITLE
Executive Vice President, Regulatory Affairs

DATE
September 3, 2002

Please note that the Small Business Waiver that has been granted for Coviracil® applies to the enclosed NDA 21-500 and not [redacted] as referenced in the attached letter.

[redacted] submitted based solely on bioequivalence data which is contained in NDA 21-500. The NDA for Coviracil Capsules, NDA 21-500 also contains clinical data to support approval for the treatment of HIV-1 Infection. In accord with FDA Guidance, "Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees", the [redacted]

Therefore, for the purposes of the Small Business Waiver, NDA 21-500 is the first human drug application that Triangle Pharmaceuticals is submitting and the application for which Triangle received the Small Business Waiver.

**APPEARS THIS WAY
ON ORIGINAL**

Division Director's Memorandum
July 1, 2003

NDA 21-500: Emtriva (emtricitabine) 200 mg capsules
Indication: Treatment of HIV
Applicant: Gilead Sciences

Background

There are currently 18 drugs (distinct molecular entities) approved for the treatment of HIV. These include seven nucleoside reverse transcriptase inhibitors (NRTI), 3 non-nucleoside reverse transcriptase inhibitors (NNRTI), seven protease inhibitors and one fusion inhibitor. Emtricitabine is an NRTI and is chemically similar to lamivudine, which is indicated for the treatment of HIV and chronic hepatitis B. Because of its activity, tolerability, and ease of administration lamivudine is recommended as a preferred component of first line HIV treatment regimens. However, resistance to lamivudine can occur quickly following a single amino acid substitution in RT, particularly if used in suboptimal HIV regimens or if adherence is poor. Given emtricitabine's chemical similarity to lamivudine, it is not surprising that these drugs have similar activity, safety and resistance profiles. The similarities and differences will be discussed in greater detail in the sections that follow.

Emtricitabine does not appear to offer any additional therapeutic benefit (including safety, efficacy, resistance profile or ease of administration) over other approved NRTI. As such, the Division determined that emtricitabine would not be a candidate for accelerated approval. Consequently, the sponsor submitted 48 week data from two controlled studies to support traditional approval.

One regulatory issue meriting mention is the fact that a phase 3 study conducted in South Africa (study 302) comparing emtricitabine with lamivudine as part of an initial HAART regimen was put on hold by both the MCC (Medicines Control Council) of the Republic of South Africa and the FDA. Participant adverse events most likely related to the use of nevirapine in that trial brought to light poor clinical study practices and some protocol violations. Consequently, the Division only reviewed safety data from this study to enhance understanding of the safety profile of emtricitabine.

Dose Selection

Dose was selected based on data from two studies in which emtricitabine was given as monotherapy for two weeks. In one of the studies emtricitabine was compared to lamivudine. An approximate tenfold range of doses was studied

including BID and QD regimens. Viral load reductions appeared to be near maximal at doses greater than or equal to 100 mg/day. At the dose chosen for marketing, 200 mg QD, antiviral activity was comparable to an approved dose of lamivudine (150 mg BID).

The selected dose is reasonable based on the data generated from the phase I and II studies. Dose determination for antiretrovirals are often based on short-term monotherapy studies. These studies allow for a "cleaner" evaluation of activity in the absence of other drugs. Longer study periods are not used because of the potential for resistance and the fear of jeopardizing future treatment options for study participants.

Efficacy

The efficacy of emtricitabine has been demonstrated in two phase 3 randomized controlled clinical studies and in several uncontrolled studies. Patients were either treatment naïve (study 303) or had demonstrated virologic suppression on an HIV treatment regimen that included lamivudine (study 301A).

In open-label study 301A, patients with HIV RNA levels less than 400 copies/mL on a HAART regimen which included lamivudine were randomized to either remain on their initial HAART regimen including lamivudine or continue their HAART regimen while substituting emtricitabine for lamivudine. At the end of 48 weeks proportions of patients maintaining HIV RNA levels less than 400 copies and 50 copies were comparable between treatment arms. Numerically the point estimate favored lamivudine slightly. However, this difference appeared to be related to a slightly higher rate of discontinuations on the emtricitabine arm. The proportions experiencing virologic rebound were the same.

In study 303, a randomized double blind, two-arm study, emtricitabine was compared to stavudine in an initial HAART regimen that also included didanosine and efavirenz. In this study the proportion of patients maintaining HIV RNA levels less than 400 and 50 copies/mL was higher on the emtricitabine arm. Part of this difference in treatment effect was mediated by a higher discontinuation rate on the stavudine arm. This is consistent with other studies that have shown that a stavudine/didanosine nucleoside backbone is less well tolerated than other nucleoside regimens. However, virologic rebound was also higher on the stavudine arm, indicating that at least part of the favorable treatment effect observed on the emtricitabine arm may have been mediated by better virologic control.

Other single arm trials evaluating the use of emtricitabine as part of initial HAART regimens including efavirenz demonstrated response rates typically observed for preferred first line HIV treatment regimens.

In brief, the antiviral activity of emtricitabine is comparable to that of lamivudine and most likely better than that of stavudine. Although the latter comparison may have been somewhat confounded by the relatively poor tolerability of stavudine and didanosine.

Resistance

The major resistance pathway of emtricitabine appears to be identical to that of lamivudine. Specifically a single amino acid substitution (I or V) in the RT at M184 confers high level resistance to both drugs.

In addition an amino acid substitution in the RT at position 65 also confers reduced susceptibility to emtricitabine. The latter mutation is relatively infrequent but may emerge after exposure to other NRTI such as tenofovir, didanosine, and abacavir.

For this reason, the product insert indication states that the use of EMTRIVA for treatment experienced adults may be considered for patients whose isolates are expected to be susceptible to EMTRIVA as assessed by genotypic or phenotypic testing.

Safety

Clinical

Overall the safety and tolerability profiles of emtricitabine are comparable to that of lamivudine, which is considered to be one of the most well tolerated antiretrovirals. Study discontinuations for emtricitabine adverse events were relatively low (ranging from 4-7%) in the phase 3 trials. The most common adverse events included headache, nausea, vomiting, diarrhea, rash and skin discoloration. All but the latter have been observed with lamivudine. Among patients receiving emtricitabine, skin discoloration occurred primarily in people of color, particularly of African descent. It was characterized by nontender palmar or plantar hyperpigmented macules. It appeared to be asymptomatic and unrelated to other rashes. A similar disorder of hyperpigmentation in people of color has been observed in individuals receiving zidovudine. Both the applicant and the FDA consulted dermatologic experts regarding this issue. Both commented that the skin discoloration appeared to have a benign course. The Division has asked the sponsor to conduct a postmarketing study to further characterize the mechanism for the skin discoloration and its clinical significance. The applicant has agreed to complete such a study.

As with other drugs active against HBV, cessation of treatment with emtricitabine can result in rebound of HBV DNA and subsequent liver inflammation. Several cases of post-treatment liver flares were observed in the emtricitabine development program. Although the safety and efficacy of emtricitabine has not been determined for the treatment of chronic hepatitis B, the label will carry a warning as to the potential for post-treatment flares. Many HIV infected patients may be co-infected with HBV. Therefore the product insert recommends routine

testing for the presence of HBV prior to initiating antiretroviral therapy. Although the label clearly states that emtricitabine is not indicated for the treatment of chronic HBV, if emtricitabine is used in an HIV/HBV co-infected patient, monitoring of liver enzymes should continue for several months after stopping emtricitabine.

As for all other NRTI, emtricitabine will carry the Box Warning regarding the potential for lactic acidosis and hepatic steatosis associated with this class of drugs.

Laboratory

Elevations of transaminases creatinine kinase were observed in patients receiving emtricitabine in clinical studies; however, the frequency and severity was similar to that observed with lamivudine.

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Recommendations

I fully concur with the clinical review and conclusions prepared by Russ Fleischer, the primary clinical analyst for this application. Emtricitabine has demonstrated safety and efficacy for the treatment of HIV and should be approved for this indication. In almost all respects, including safety, efficacy and resistance, emtricitabine is comparable to lamivudine, a previously approved NRTI. The availability of emtricitabine will provide for an NRTI option in constructing an HIV regimen, primarily in patients with limited treatment experience. Since emtricitabine and lamivudine are completely cross resistant and since the characteristic mutation (M184V) often occurs prior to other resistance mutations, emtricitabine may not be useful in patients who have failed prior regimens including lamivudine.

Skin discoloration, likely a benign phenomenon, has been observed primarily in people of color. This is not a characteristic adverse event associated with lamivudine; however, similar patterns of hyperpigmentation have been observed with zidovudine. The applicant has committed to investigating the mechanism and clinical course of skin discoloration in postmarketing studies.

Although emtricitabine is primarily renally eliminated, the applicant has also agreed to further evaluate its enzymatic metabolism.

As with most antiretrovirals, the approval of emtricitabine includes a patient package insert. Other than product insert warnings, notably regarding the

potential for lactic acidosis/hepatic steatosis and post-treatment liver flares, no additional risk communication procedures are warranted at this time.

/S/

Jeffrey S. Murray, M.D., M.P.H.
Deputy Division Director
DAVDP/ODE4

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Jeffrey Murray
7/2/03 08:25:04 AM
MEDICAL OFFICER

Mark Goldberger
7/2/03 12:21:25 PM
MEDICAL OFFICER

Demographic Worksheet

Application Information (Enter all identifying information for the submission pertaining to this summary)

NDA Number: 21-500

Submission Type: N/A (pilot)

Serial Number: N/A (pilot)

Subgroups Included In Application (Please provide information for each category listed below from the primary safety database excluding PK studies)

CATEGORY		NUMBER EXPOSED TO STUDY DRUG		NUMBER EXPOSED TO STUDY DRUG		NUMBER EXPOSED TO STUDY DRUG	
Gender	Males	<u>1087</u>		All Females	<u>600</u>		Females >50
Age:	0-≤1 Mo.			>1 Mo.-≤2Year			>2-≤12
	12-16			17-64	<u>1680</u>		≥65
							<u>< 1%</u>
Race:	White	<u>530</u>		Black	<u>800</u>		Asian
<u>HISPANIC</u>	Other	<u>90</u>					<u>129</u>

Gender-Based Analyses (Please provide information for each category listed below.)

Category	Was Analysis Performed?			
	If no is checked, indicate which applies or provide comment below			
Efficacy	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Inadequate #'s	<input type="checkbox"/> Disease Absent
Safety	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Inadequate #'s	<input type="checkbox"/> Disease Absent

Is a dosing modification based on gender recommended in the label?

If the analysis was completed, who performed the analysis

Was gender-based analysis included in labeling?	
YES	No
<input type="checkbox"/>	<input checked="" type="checkbox"/>
<input type="checkbox"/>	<input checked="" type="checkbox"/>

Yes

No

Sponsor

FDA

Age-Based Analyses (Please provide information for each category listed below)

Category	Was Analysis Performed?			
	If no is checked, indicate which applies or provide comment below			
Efficacy	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Inadequate #'s	<input type="checkbox"/> Disease Absent
Safety	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Inadequate #'s	<input type="checkbox"/> Disease Absent

Is a dosing modification based on age recommended in the label?

If the analysis was completed, who performed the analysis

Was age-based analysis included in labeling?	
YES	No
<input type="checkbox"/>	<input checked="" type="checkbox"/>
<input type="checkbox"/>	<input checked="" type="checkbox"/>

Yes

No

Sponsor

FDA

Race-Based Analyses (Please provide information for each category listed below)

Category	Was Analysis Performed?			
	If no is checked, indicate which applies or provide comment below			
Efficacy	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Inadequate #'s	<input type="checkbox"/> Disease Absent
Safety	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Inadequate #'s	<input type="checkbox"/> Disease Absent

Is a dosing modification based on race recommended in the label?

If the analysis was completed, who performed the analysis

Was race-based analysis included in labeling?	
YES	No
<input type="checkbox"/>	<input checked="" type="checkbox"/>
<input type="checkbox"/>	<input checked="" type="checkbox"/>

Yes

No

Sponsor

FDA

In the comment section below, indicate whether an alternate reason (other than "inadequate numbers" or "disease absent") was provided for why a subgroup analysis was NOT performed, and/or if other subgroups were studied for which the metabolism or excretion of the drug might be altered (including if labeling was modified).

Comment:



RECORD OF INTERNAL MEETING

MEETING DATE: May 19, 2003

TIME: 11a.m. **LOCATION:** Corporate S400

REVIEW DIVISION: HFD-530, Division of Antiviral Drug Products (DAVDP)

NDA: 21-500
Drug: emtricitabine capsules
Proposed Indication: Treatment of HIV-1 infection
Applicant: Gilead Sciences

Type of Meeting: Pre-approval Safety Conference

ODE 4 Participants:

Mark J. Goldberger, M.D., Director
Ed Cox, M.D., Deputy Director
David Roeder, M.S., Associate Director for Regulatory Affairs

DAVDP Participants:

Debra Birnkrant, M.D., Director
Russ Fleischer, PA-C, M.P.H., Medical Reviewer
Pritam Verma, Ph.D., Pharmacology/Toxicology Reviewer
Virginia L. Yoerg, Regulatory Health Project Manager

ODS Participants:

Allen Brinker, M.D., Medical Officer/Epidemiology
Melissa Truffa, Safety Evaluator
Debbie Boxwell, Safety Evaluator (on telephone)
Quynh Nguyen, Regulatory Project Manager

Meeting Objective: To provide an update to the Office of Drug Safety regarding the emtricitabine safety issues prior to NDA approval.

Background: Emtricitabine, also known as FTC, is a nucleoside reverse transcriptase inhibitor. The proposed dose of emtricitabine is one 200 mg capsule administered once daily (QD).

Two Phase 3 studies were considered in this NDA as support for the safety and efficacy of emtricitabine. Clinical trial FTC-301A directly compared emtricitabine to stavudine on a background of didanosine and efavirenz in treatment naïve patients, and was conducted in

the United States, Canada, Mexico, Chile, Brazil, Argentina, United Kingdom, France, and Germany. Clinical trial FTC-303 evaluated the equivalence of emtricitabine to lamivudine in HIV-1 infected adults who had virologic suppression on a lamivudine-containing regimen in the United States.

This NDA was submitted on September 3, 2003 and the PDUFA goal date is July 3, 2003.

Discussion:

Mr. Fleischer briefly summarized the efficacy results and presented the following safety information:

More than 2500 HIV and hepatitis B virus (HBV) infected adults have been exposed to emtricitabine (200 mg, QD) for up to 48 weeks or more. Emtricitabine is generally well tolerated and the safety profile is comparable to lamivudine. This result was expected, since emtricitabine is structurally similar to lamivudine.

Safety Considerations:

- **Adverse Events (AEs)/ Serious Adverse Events (SAEs).** The most common adverse events were headache, nausea, vomiting, diarrhea, rash, and elevated AST and ALT.
- **Lactic Acidosis.** This is a nucleoside-related toxicity. A boxed warning will be included in the emtricitabine label, which will have identical wording to the boxed warnings addressing lactic acidosis included in all nucleoside transcriptase inhibitor labels.
- **Pregnancy.** 53 pregnancies occurred in women exposed to emtricitabine, and 19 live healthy births were reported. Most of the pregnancies were terminated, and there were six spontaneous abortions. Emtricitabine is labeled as Pregnancy Category B.
- **Skin discoloration.** Skin discoloration, manifested by hyperpigmentation on the palms and/or soles, was predominantly observed in non-Caucasian patients. The mechanism of action and clinical significance were not explained. Since DAVDP received minimal data regarding this adverse event, DAVDP will request more information from the applicant.
- **Exacerbation of hepatitis.** Exacerbations of hepatitis were reported in patients (co-infected with HIV and Hepatitis B) after discontinuation of emtricitabine.

Actions:

- DAVDP will request more information from the applicant regarding the skin discoloration seen primarily in black patients.

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this page is the manifestation of the electronic signature.**

/s/

Debra Birnkrant
7/1/03 11:48:21 AM



RECORD OF DAVDP/INDUSTRY TELECON

Date of Teleconference: May 8, 2003
NDA: 21-500
Drug: emtricitabine capsules for HIV
Sponsor: Gilead Sciences, Inc. (Gilead)

DAVDP Participants:

Russ Fleischer, PA-C, M.P.H., Medical Reviewer
Stephen P. Miller, Ph.D., Chemistry Team Leader
George Lunn, Ph.D., Chemistry Reviewer (on telephone)
Virginia L. Yoerg, Regulatory Health Project Manager

Gilead Participants:

Taiyin Yang, Vice President, Manufacturing
Ernie Prisbe, Vice President, Chemical Development
Martine Kraus, Director, Regulatory Affairs
David Upchurch, Associate Director, Chemical Development

Subject: Addition of manufacturing site at _____

Background:

This teleconference was held to discuss Gilead's May 1, 2003 proposal to submit an additional manufacturing site for emtricitabine API. Gilead wanted to amend NDA 21-500 to include _____ as a second site for the manufacture of emtricitabine API, and requested feedback from DAVDP as to the acceptability of their proposal.

Discussion:

DAVDP stated that the applicant may submit an amendment to the NDA, requesting the addition of another manufacturing site in _____. However, DAVDP cannot determine if the site will require an inspection. If CDER's Office of Compliance deems that an inspection is necessary, the submission will be considered a major amendment to the NDA, and the PDUFA clock would be extended by three months (October 3, 2003 instead of July 3, 2003).

Gilead noted that the _____ site was inspected for a pre-approval inspection for _____ in July, 2002 and was found acceptable. Gilead indicated that if FDA determines that an inspection is necessary for the additional manufacturing site, they would withdraw the amendment in order to prevent an extension of the review period, and would resubmit the amendment after approval as a CMC amendment to the approved NDA.

_____ is currently listed in the NDA as the sole manufacturer of emtricitabine API. DAVDP asked Gilead if the addition of the _____ site is critical for sufficient supply of emtricitabine API to meet launch and subsequent commercial demand for emtricitabine capsules. Gilead stated that launch is possible with use of the _____ facility as their sole source of the API; however, the launch processes would have to be cautiously managed with _____. Gilead also noted that they plan to utilize the _____ site as their major supplier following the approval of emtricitabine. CDER's Office of Compliance inspected the _____ facility in December 2002. Gilead agreed to submit a copy of _____ response to the Office of Compliance report to DAVDP.

Gilead described _____ ongoing process validation and indicated that _____ plans to contact the District Office regarding a follow-up inspection when validation is nearing completion (end of May, 2003).

Actions:

- The applicant will submit a copy of _____ response to the Office of Compliance report to DAVDP.
- Gilead will submit the _____ site as an alternate API manufacturing site.
- DAVDP will review the amendment and submit the amendment to EES. If this site requires an inspection, the PDUFA clock will be extended by three months.
- DAVDP and Gilead agreed to monitor the inspection status for the testing facilities, and will hold a teleconference if timing becomes critical.

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this page is the manifestation of the electronic signature.**

/s/

Virginia Yoerg
5/21/03 01:45:51 PM
CSO

hard copy signed

Stephen Paul Miller
5/21/03 02:12:12 PM
CHEMIST



RECORD OF FDA/INDUSTRY MEETING

Date of Meeting: July 3, 2002
IND:
Drug: Coviracil® (emtricitabine)
Sponsor: Triangle Pharmaceuticals
Indication: Treatment of HIV-1 infection
Type of Meeting: Pre-NDA Meeting

FDA Participants:

Mark J. Goldberger, M.D., M.P.H., Office Director, ODEIV
Debra B. Birnkrant, M.D., Division Director
Jeffrey S. Murray, M.D., M.P.H., Deputy Division Director
Steven Gitterman, M.D., Medical Team Leader
Russell Fleischer, PA-C, M.P.H., Senior Clinical Analyst
George Lunn, Ph.D., Chemist
James G. Farrelly, Ph.D., Pharmacology Team Leader
Pritam Verma, Ph.D., Pharmacologist
Narayana Battula, Ph.D., Microbiologist
Arzu Selen, Ph.D., Acting Pharmacokinetics Team Leader
Robert O. Kumi, Ph.D., Pharmacokinetics Reviewer
Greg Soon, Ph.D., Biometrics Team Leader
Susan Y. Zhou, Ph.D., Mathematical Statistician
David L. Roeder, Associate Director, Regulatory Affairs, ODEIV
Sean Belouin, R.Ph., Regulatory Project Manager
Nitin Patel, R.Ph., Regulatory Project Manager

External Participants:

Anne McKay, VP Regulatory Affairs
Joseph Quinn, MSPH, VP Biometrics and Project Leader
Franck Rousseau, M.D., VP Medical Affairs
Charles Wakeford, Ph.D., Director Biometrics

BACKGROUND:

This pre-NDA meeting was held at the request of the Sponsor, Triangle Pharmaceuticals. The Sponsor submitted a pre-NDA background data package on May 31, 2002 (SN493). This package included a proposed agenda, a draft package insert, draft summaries of all technical sections of the NDA, and specific questions. Prior to the meeting the Sponsor submitted three additional questions by electronic mail to Mr. Patel, the Regulatory Project Manager, on June 26, 2002. These additional questions were posed in light of the preliminary 24-week blinded analysis from the ongoing Phase III clinical study, FTC-301A.

DISCUSSION:

The Sponsor provided a brief update concerning the deliberations of the Data Safety Monitoring Board (DSMB) for study FTC-301A. The Sponsor said that two of the three members of the DSMB determined that the study should be stopped and unblinded, and those patients on the inferior arm should be allowed to roll-over to the superior arm. A final recommendation will be made after concurrence from the third member, who was out of the country and not available. The Division acknowledged the recommendation of the DSMB. In a later discussion concerning the results of FTC-301A, it was agreed that the Sponsor should review the analysis using the statistical algorithm (Attachment A) provided by the Division, to ensure that there would not be any difference in interpretation of the study results with regard to the decision to unblind the trial.

The meeting then pertained to the questions provided by the Sponsor to the Division. Please note, the Sponsor's questions and proposals are shown in regular font, followed by the Division's response in bold font.

List of questions and proposals:

1. Will the Division accept pre-submission of completed technical sections of the NDA?

The Division agreed to accept pre-submission of all technical sections. The Division will accept for submission only a complete section of the NDA, such as the entire CMC section, or toxicology section. The Division asked the Sponsor to provide a schedule or timeline for submission of the completed technical sections.

- 2.

Item-Specific NDA Questions:

3. ITEM 2 – Labeling

We plan to provide the package insert in the current format and not in the format described in the proposed rule issued December 2000 for prescribing information. Is this acceptable?

The Division was in agreement that this was acceptable.

4. ITEM 4 – Chemistry, Manufacturing and Controls

We do not plan to have any issues to discuss on Item 4 during the pre-NDA meeting. If the FDA allows the presubmission of the technical sections, Item 4 could be submitted in July.

The Division agreed to accept pre-submission of the CMC section of the NDA. In the CMC section, the Division asked the Sponsor to spell out the responsibilities for each manufacturing site and state when they will be ready for inspection. The Division asked the Sponsor to verify that 12 months of stability data for 3 batches of drug product will be available at the time of NDA submission. The Division reminded the Sponsor that we have yet to reach agreement on the starting materials. However, the Sponsor should not delay the pre-submission of the CMC section for this reason. Agreement on the starting materials can be reached during the normal course of the NDA review.

5. ITEM 5 - Nonclinical Pharmacology and Toxicology

We propose to file the Item 5 Overall Summary and cross-reference the IND submission dates and serial numbers of all preclinical reports submitted to the IND. Please confirm if this is still acceptable?

The Division advised that the proposal to not resubmit the preclinical studies is acceptable, however, the Division may request individual studies as needed.

6. ITEM 6 – Human Pharmacokinetics and Bioavailability

In correspondence dated August 25, 1999, the FDA requested relevant electronic data sets for all studies included in Item 6 be submitted in the NDA. The suggested format was in Microsoft Excel or ASCII. We plan to provide the electronic files as requested above from the August 25, 1999 correspondence and can provide sample tables upon request. Could the Division please confirm that this is still the desired format for Item 6?

The Division advised that the current guidelines require that electronic files be in SAS transport file format.

7. ITEM 8 – Clinical Data

Please see Tables 1 and 2 under Item 8 – Clinical Data Section for the listing of clinical studies to be included in the NDA. We have also listed the studies that will be included in the Integrated Summaries of Safety (ISS) and Efficacy (ISE) and request your review of this proposal. Also please note that where final study reports are not available from recently completed, ongoing, or supportive studies, synopses of key efficacy and safety findings will be provided, if available, or patient disposition, SAE's and study status. This information has been noted on Tables 1 and 2.

Triangle will provide SAE narratives (paper copy only) in the final study reports for all SAEs from completed studies. For ongoing studies or where only a synopsis of the results are available, the SAE narratives will be provided in the ISS. For ongoing study FTC-301A which will not be included in the ISS, SAE narratives will be provided with the 24-week report.

The Division advised that the studies proposed to be included in the Integrated Summaries of Efficacy and Safety are acceptable as outlined in Tables 1 and 2 of the pre-NDA background data package (SN493).

The Division requested that narratives for SAE's, deaths, and all withdrawals in studies FTC-301 and 301A, FTC-302, and FTC-303 be submitted.

8. ITEM 9 – Safety Update Report

In our submission of February 13th we proposed that the 48-week FTC-301A report and the 120 day safety update be submitted at the same time. As requested by FDA, this submission will be made within 4 months of the original application

Within 4 months of the NDA submission, we will submit the final 48-week report for clinical study FTC-301.

With regard to the data to be provided in the 120 day safety update, we propose to include any new SAE's from ongoing studies and for study FTC-301A, all new clinical adverse events and laboratory abnormalities in addition to new SAE's.

The Division was in agreement that this proposal was acceptable.

9. ITEM 10 - Statistical

We propose to submit an exact paper copy of Item 8 as Item 10 except in the appropriate color binders.

In addition to the SAS data sets of the raw data, the Division requested to receive the analysis SAS datasets and the SAS programs used to construct the analysis data sets. Additionally, the Division requested copies of the SAS programs used for the analysis of the efficacy endpoints. The main efficacy analysis that will appear in the labeling will be based on the algorithm that was provided at the meeting (Attachment A). The Sponsor will need to include analyses using this algorithm in the NDA for studies FTC-301 and FTC-303.

10. ITEM 11 - Case Report Tabulations

Integrated Summary of Efficacy (ISE) and Integrated Summary of Safety (ISS) Listings
We propose to not include any CRF domain data listings in the ISS or ISE. There will be supporting data listings as necessary to show individual patients with specific outcomes of interest, e.g. deaths, withdrawal due to AE, etc. These supporting data listings will be provided as paper copies.

The Division was in agreement that this proposal was acceptable.

Clinical Study Report Datasets/CRF Domain Datasets

Triangle proposes to submit the CRF domain datasets (and analyses datasets) only for studies FTC-301A (24 week), FTC-302, and FTC-303 in electronic format. Paper data listings will not be submitted for these studies. For all other full study reports included in the NDA, paper copies of the domain listings will be provided.

For studies where a study synopsis will be provided (i.e. MKC-401) paper copies of necessary supporting data listings will be included. No domain data listings or SAS data sets will be provided for these studies.

The Division was in agreement that this proposal was acceptable. The Division advised that any data submitted electronically must be in accordance with the guidance for electronic submissions.

Triangle requests a waiver on submission for patient profiles.

The Sponsor clarified that their patient profile is basically a condensed summary of individual patient data collected on the Case Report Form. The Division agreed that a waiver was acceptable, but stated that there may be some additional requests of these data once the application is received.

11. ITEM 12 - Case Report Forms

We propose to submit in the NDA all CRFs for Deaths and Withdrawals Due to AE for all HIV and HBV studies, completed and ongoing in electronic format per FDA guidelines. In addition, we propose to submit the CRFs for all SAEs in the four Phase III studies; FTC-303, FTC-302, FTC-301, and MKC-401 electronically. (For ongoing studies, CRFs available as of 01MAY02 will be submitted)

For the PACTG, ACTG, and ANRS studies we will request CRFs for deaths and withdrawals due to adverse events. The respective collaborative groups manage these studies and Triangle does not have direct access to the CRFs or the study databases although we do receive Adverse Events and Serious Adverse Event (SAE) information on an ongoing basis. Because the ANRS study CRFs are in French, Triangle will provide translated versions of the blank CRFs for the 2 studies, ANRS 091 (Montana) and ANRS 099 (Alize). For submitted CRFs, translations of text fields will be provided within each individual pdf file.

The Division was in agreement that this proposal was acceptable. The Division stated that additional CRFs may be requested during the review.

Additional questions based on FTC-301A data:

12. Assuming that the superior treatment arm of study FTC-301A is the experimental arm (i.e. FTC), does the Agency agree that the trial has met the regulatory objective of proving non-inferiority of FTC to the d4T control arm?

If yes, does the Agency agree that the current Week 24 (N=571) and Week 48 (N=299) results are compelling enough to satisfy the regulatory requirements for traditional approval? This would mean that the final review would not require an update within 4 months of the NDA submission.

The Sponsor was advised that this issue cannot be addressed until the Division reviews the data. Additionally, the Division will require the 48-week data from study FTC-301 prior to making a decision on the trial. The Division indicated that the amount of 48-week data may be negotiated once the Division reviews the Week 24 report and assesses the quantity of 48-week data available. The Division also stated that the FTC-301A report should be submitted with unblinded data.

13. Assuming that the superior treatment arm of study FTC-301 is FTC, Triangle believes that it should qualify for a priority review based on showing a significant improvement compared to a marketed product. Improvement is demonstrated by evidence of increased effectiveness in the treatment of HIV-1 compared to d4T and FTC also is taken once daily which has been documented to enhance patient compliance.

Will the Agency consider granting the FTC NDA priority review?

The Division advised that it does not believe that FTC qualifies for a priority review because once-daily dosing is no longer considered a rationale for priority review. Additionally, although FTC-301 may show superiority, the Division will review the application in totality, including the FTC-303 equivalency results to determine if the drug qualifies for priority review. The Division advised the Sponsor to make its best argument for priority review in the NDA and the decision will be made at the 45-day filing meeting.

14. Assuming that the superior arm of study FTC-301A is FTC, does the Agency agree that adequate safety and efficacy have been demonstrated to support an expanded access program of FTC 200 mg QD in order to facilitate a once daily HAART regimen?

The Division was concerned about an expanded access program for the general naïve population only to facilitate a once-daily medication. The Division was open to the possibility for an expanded access program targeting a specific niche of the population in which there is a defined need. The Division advised that the Sponsor may propose a program for a subgroup of patients who could benefit.

ACTIONS:

The Sponsor will review the analysis of the results of study FTC-301A, using the statistical algorithm (Attachment A) provided by the Division.

Minutes Preparer: Nitin Patel, R.Ph., Regulatory Project Manager
Date: July 17, 2002

**APPEARS THIS WAY
ON ORIGINAL**

ATTACHMENT A

- Please provide details in generating efficacy results. Please describe whether there are repeated HIV RNA measurements per subject per visit using one or more assays. If any, please discuss how these repeated measurements were combined into a single value.
- Please perform efficacy analyses for HIV RNA level LOQ=400 c/mL and then LOQ=50 c/mL using the attached new Time to Loss-of-Virologic Response (TLOVR) algorithm (see A2.) for Study FTC-303 and Study FTC-301A, respectively. This request is based on the fact that the Division of Antiviral Drug Products (DAVDP) currently modified the definition of viral failure.

The details of the requested efficacy analyses are listed below.

1. Calculate TLOVR using the attached TLOVR algorithm and plot the corresponding Kaplan-Meier survival curves through Week 48 and beyond by treatment arms.
If quality data beyond Week 48 are available then the TLOVR analysis should be extended beyond Week 48.
2. Calculate the response rates using the attached definitions for each visit through Week 48 for each treatment arm (see A1).
For visits beyond Week 48, response rates derived from the Kaplan-Meier estimate should be used.
3. Plot the response rates over time for treatment arms.
The number of patients not censored by each visit (including patients still in trial + patients who have failed earlier) should be displayed at the bottom of the graph by the treatment arms.
4. Provide time and reasons for permanent discontinuation of study drug, adding new medications and loss to follow-ups. If there are multiple reasons then they should all be accounted for. In addition, please describe the adverse events at the time of study discontinuation, adding new medications or loss to follow-up. Please explain the associations between the adverse events and deaths.
5. Classify Week 48 failures according to the primary reason for the earliest failure where the time should be determined by the TLOVR.

For subjects who failed for multiple reasons at the earliest time for failure, the order for classifications is death, virologic failure, AE, and then other reasons. For example, if virologic rebound and AE resulting in discontinuation occurred at the same visit, then the patient would be classified as a virologic failure. However, if a patient discontinued due to an AE and subsequently died, then the reason for failure would be death, if the death were reasonably attributed to that AE.

6. Display the information in Step 5 in a table formatted as in A4. Table 1 below. Also, provide p-value for testing the difference in proportion of subjects with < LOQ between the two treatment arms.

The current algorithm does not treat disease progressions as failures if such events did not cause discontinuation of the study drug or introduction of new anti-retroviral drugs. If all disease progressions need to be counted as failures then the following should be added as a

separate item:

Repeat 1-6 above counting new CDC Class C events as failures in the algorithm (the current algorithm does not regard CDC Class C events as failures unless it leads to discontinuation of study or introduction of new anti-retroviral drugs to the regimen).

7. Provide detailed description for each patient that died or experienced a new CDC Class C event, including those that did not lead to study discontinuation or change of therapy. Note Table 1 in A4 contains only those new CDC Class C events that led to study discontinuation and/or addition of new anti-retroviral drugs.

Please provide a separate dataset containing the information on these patients. The information should include Protocol, Patient ID, Treatment assigned, Treatment received, all stratification variables, Time of event, and Description of event.

A1. Definitions for a Non-responder (failure)

For each visit, a subject with the following events prior to or at this visit will be considered as a non-responder or failure for that visit (see details in attached A2. TLOVR algorithm) if any of the follow occur:

- 1) Death
- 2) Permanent discontinuation of the study drug or Loss to follow-up
- 3) Introducing a new drug to the regimen
- 4) Have not achieved <LOQ that was confirmed later or achieved confirmed <LOQ status but rebounded (i.e., two consecutive \geq LOQ copies/mL (the latter one possibly after the visit of interest) or one \geq LOQ copies/mL for the last available visit).

From the above definitions for a non-responder or failure, a subject who is not a non-responder or failure will be regarded as a responder. In other words, responders are those who had achieved viral load <LOQ that is confirmed later prior to or at the visit of interest, but had not yet lost the virological response defined by the TLOVR algorithm below.

Never treated may be included as a failure for some trials.

A2. Time to Loss-of-Virologic-Response (TLOVR) Algorithm

For studies with at least 48 weeks virologic data, one analysis that computes time to virologic failure should follow the algorithm below.

- 1) For 2) and 3) below, discard all visits with no data. In what follows, a visit means a visit with an observed viral load. Viral load data from all available visits, including off-schedule visits and post Week 48 visits, should be included for the calculation.
- 2) If a subject had never achieved confirmed HIV RNA levels below the assay limit (on two consecutive visits) before the following events, then this subject will be considered to have failed at time 0:
 - 2.1. Death
 - 2.2. Permanent discontinuation of the study drug or loss to follow-up
 - 2.3. Introduction of a new anti-retroviral drug to the regimenWith FDA agreement at design stage, exceptions may be made for certain background drug changes where the reason for the change is due to either toxicity or intolerance that

can be clearly attributed to the background drug, but not the study drug or its control. Such exceptions should be incorporated into the protocol.

- 2.4. Last available visit.
- 3) For all subjects who had confirmed HIV RNA levels below an assay limit, i.e., on two consecutive visits below assay limit, the time of failure is the earliest time when a specific event had occurred. Those events are modifications in 4) and are listed below:
- 3.1. Death
 - 3.2. Permanent discontinuation of the study drug or loss to follow-up
 - 3.3. The event as described in 2)2.3.
 - 3.4. Confirmed HIV RNA levels above or equal to an assay limit
Defined as HIV RNA levels from two consecutive visits are greater than or equal to an assay limit or one visit greater than or equal to an assay limit followed by Permanent discontinuation of the study drug or loss to follow-up.
- 4) If the time of virologic failure defined above is immediately preceded by a single missing scheduled visit or multiple consecutive missing scheduled visits, then the time of virologic failure is replaced by the first time of such missing visits.

For open-label studies, or studies that blinding is difficult to maintain due to regimen-specific observable events (for example rash, headache, diarrhea, etc.), algorithms that incorporate other ways of handling missing data or treatment changes may be used for additional sensitivity analyses.

For example, sponsors should perform analyses that explore the sensitivity of the results to potential biases related to such trials. One such analysis should treat all patients who meet the protocol-defined criteria for treatment changes (for example, protocol defined virological failure, insufficient viral load response, immunologic failure, disease progression, etc.) as failures, while the non protocol-specified treatment changes are treated as failures in the study arm, and as censored at the time of change in the control arm.

A3. Considerations When Using This Algorithm

1) Re-suppressions

The use of this algorithm makes the assumption that after receiving the treatment regimen, each patient's true viral load will experience a decrease first, and then eventually a rebound, i.e., the true viral load curve is "U" shaped.

After confirmed viral rebound, some patients may achieve confirmed suppression again and maintain that suppression, seemingly violating the 'U' shape. A few such cases are expected due to the following reasons:

1. Assay variability. This creates both false suppressions and false rebounds. This happens when a patient's viral load hovers around the assay limit for an extended period of time.
2. Temporary dose reduction or discontinuation of a drug to resolve problems such as an adverse event or tolerability. Most of the times this problem can be resolved by requiring the confirmation visit to be a few weeks after the visit that the viral load first suppressed or rebounded. The applicant can incorporate this requirement into the algorithm.

If many such events were observed, then it may suggest other mechanisms. This could also occur due to trial design features (systematic treatment interruptions). In these cases the algorithm may not be appropriate. Alternative approaches should be proposed and discussed with FDA.

2) Discontinuation of study vs. permanent discontinuation of study drug

Substitution of “permanent discontinuation of study drug” with “discontinuation of study” in the algorithm may be desirable for trials that have good collection of information on if additional drugs have been taken by a patient after permanent discontinuation of study drug. The sponsor may propose and discuss with FDA for such a change.

A4. Table 1. Summary of Study Outcomes

The following table will be used to assist the reviewing and drafting of the label. It is not a proposal for label.

Table 1. Summary of Study Outcomes

Outcome	Study Regimen ⁵ (N=) ⁴		Control ⁵ (N=) ⁴	
	n	%	n	%
Responder ¹				
Virologic failure				
Never suppressed through Week 48 and on study at Week 48				
Rebound				
Discontinued study drug or added new drugs due to virologic failure ²				
Discontinued study drug or added new drugs due to insufficient viral load response ²				
Discontinued study drug or added new drugs before achieving confirmed suppression due to ³				
Death or events that leading to death				
Disease progression				
Immunological failure ²				
Adverse Events				
Loss to follow-up				
Consent withdrawn				
Non-compliance				
Pregnancy				
Protocol violation				
Not discontinued or not known if discontinued, but no data at Week 48 and beyond				
No post baseline blood sample				
Other				
Discontinued study drug or added new drugs while suppressed due to ³				

Death or events that leading to death		
Disease progression		
Immunological failure ²		
Adverse Events		
Loss to follow-up		
Consent withdrawn		
Non-compliance		
Pregnancy		
Protocol violation		
Not discontinued or not known if discontinued, but no data at Week 48 and beyond		
Other		
Never Treated		
<p>1 P-value= ...</p> <p>2 According to case report forms. If not conforming to the protocol-defined criteria for vorologic failure, insufficient viral load response, or immunological failure, then details should be provided for each of the non-conforming patient.</p> <p>3 The categories could be changed based on the trial results</p> <p>4 Do not include never treated in the total unless specifically requested</p> <p>5 Replace with actual regimens. For example, "FTC+ddi+EFV" and "3TC+ddi+EFV".</p>		

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/s/

Virginia Yoerg

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MEMORANDUM OF INTERNAL MEETING

Date of Meeting: October 21, 2002

NDA: 21-500

Drug: Coviracil® (emtricitabine) Capsules

Applicant: Triangle Pharmaceuticals, Inc.

Indication: Treatment of HIV-1 infection

Participants: Debra B. Birnkrant, M.D., DAVDP Director
Jeffrey Murray, M.D., DAVDP Deputy Director
Anthony W. DeCicco, R.Ph., Chief, Project Management Staff
Steven Gitterman, M.D., Medical Team Leader
Russell Fleischer, PA-C, M.P.H., Senior Clinical Analyst
Andrea James, M.D., Medical Officer
Stephen Miller, Ph.D., Chemistry Team Leader
George Lunn, Ph.D., Chemist
Greg Soon, Ph.D., Biometrics Team Leader
Susan Y. Zhou, Ph.D., Mathematical Statistician
Kellie S. Reynolds, Pharm.D., Biopharmaceutics Team Leader
Jennifer DiGiacinto, Pharm.D., Pharmacokinetics Reviewer
James G. Farrelly, Ph.D., Pharmacology Team Leader
Pritam Verma, Ph.D., Pharmacologist
Jules O'Rear, Ph.D., Microbiology Team Leader
Narayana Battula, Ph.D., Microbiology Reviewer
Antoine El-Hage, Ph.D., Branch Chief, Division of Scientific
Investigations
Nitin Patel, R.Ph., Regulatory Project Manager

Type of Meeting: Filing Meeting

Related Documents: IND [redacted] and NDA 21-500

Background

On May 31, 2002, Triangle Pharmaceuticals submitted a briefing package and requested a pre-NDA meeting. This package included a draft package insert, draft summaries of all technical

sections of the NDA, and specific questions. The pre-NDA meeting was held on July 3, 2002. At this meeting, the Division agreed to accept pre-submission of all technical sections of the NDA. The applicant first pre-submitted both the Nonclinical Pharmacology and Toxicology Section, and the Clinical Microbiology Section on July 22, 2002. Additional pre-submissions were dated July 30, 2002 and August 20, 2002. The final pre-submission which triggered the PDUFA clock was dated and received September 3, 2002. The applicant has received a small business waiver of the application fee. The internal action goal date for this NDA is early April, 2003 and the ten month PDUFA date is July 3, 2003.

This NDA is for Coviracil® (emtricitabine) Capsules for the treatment of HIV-1 infection, in combination with other antiretroviral agents. This meeting was held to determine whether the application is filable.

Discussion

1. Pharmacology/Toxicology

Dr. Verma stated that the NDA is filable.

2. Microbiology

Dr. Battula stated that the NDA is filable. He was unable to locate data on the emergence of HIV resistance for the clinical studies that were submitted in the application. A request for this information will be made to the applicant by telephone facsimile.

3. Chemistry

Dr. Lunn stated that the NDA is filable.

4. Biopharmaceutics/Clinical Pharmacokinetics

Dr. DiGiacinto stated that the NDA is filable.

5. Clinical

Mr. Fleischer stated that the NDA is filable.

6. Statistics

Dr. Zhou stated that the NDA is filable.

7. Standard or Priority Review

The applicant requested a priority review and submitted a rationale for priority review. The Division considered this rationale, but determined that the application would be granted a standard review.

8. Advisory Committee Meeting

The Division determined that an advisory committee meeting is not necessary.

9. Division of Scientific Investigations (DSI)

A consult will be sent to DSI, requesting inspection of clinical sites essential for NDA approval, and that the Inspection Summary Results be provided by April 3, 2003.

Conclusions

- The review team concluded that NDA 21-500 is filable, and is designated as a standard review (ten month clock).

Action Items

- A consult will be sent to the Office of Drug Safety (ODS) for tradename review.
- A request for information on the emergence of HIV resistance will be made to the applicant by telephone facsimile.
- The applicant will be notified of the application's filability, PDUFA action date, and that a standard review was granted.

Minutes Preparer: Nitin Patel, November 7, 2002

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/s/

Steven Gitterman
11/29/02 03:59:56 PM

Executive CAC
3/13/2001

Committee: Joseph DeGeorge, Ph.D., HFD-024, Chair
Joseph Contrera, Ph.D., HFD-901, Member
Bob Osterberg, Ph.D., HFD-520, Alternate Member
Jim Farrelly, Ph.D., HFD-530, Team Leader
Pritam S. Verma, Ph.D., HFD-530, Presenting Reviewer

Author of Draft: Pritam Verma, Ph.D.

The following information reflects a brief summary of the Committee discussion and its recommendations. Detailed study information can be found in the individual review.

The committee did not address the sponsor's proposed statistical evaluation for the 2-yr carcinogen bioassays, as this does not affect the sponsor's ability to initiate the bioassays. The sponsor may seek guidance on the statistical evaluation of bioassay results from agency staff separately. Data files should be submitted electronically following section E of the 'Guidance for Industry, Providing Regulatory Submission in Electronic Format, New Drug.'

IND #:

Drug Name: Coviracil (Emtricitabine), FTC

Sponsor: Triangle Pharmaceuticals, Inc., Durham, NC 27707

Contact Person: Anne McKay (Phone: 919-402-1117; Fax: 919-493-5925)

Background:

Rat Dose Selection- Sponsor's Proposal:

A 2-year carcinogenicity study in CD rats was proposed. Eighty rats/sex/dose will receive FTC at dose levels of 0, 60, 200 or 600 mg/kg/day. Dose selection was based on the 13-week oral gavage toxicity study in which rats were dosed with FTC at dose levels of 0, 120, 600 or 3000 mg/kg/day. All doses were well tolerated. There were no treatment related gross or histopathologic alterations. FTC was negative in a standard battery of genotoxicity assays. The pharmacokinetic characteristics of FTC were similar in rats and humans. The AUC values in the rat study were: 67.5 (low), 345.5 (mid) and 1461 microgram*hr/ml at the high dose. FTC is being administered once daily at a dose level of 200 mg/day (AUC_{ss} = 9.6 microgram*hr/ml). The sponsor has utilized the toxicokinetic endpoint (AUC) for the determination of the high dose that meets the criterion in the ICH Guideline regarding acceptability of 25 times exposure as being adequate. Thus, a dose level of 600 mg/kg/day in rats is expected to provide systemic exposures approximately 36 times the human exposure. The low and mid doses were arithmetically determined, with the low and mid doses expected to provide approximately 3 and 9 times the human exposure, respectively.

Mouse Dose Selection-Sponsor's Proposal:

A 2-year carcinogenicity study in CD-1 mice was proposed. One hundred mice/sex/dose will receive FTC at dose levels of 0, 75, 250 or 750 mg/kg/day. Dose selection was based on the 26-week oral gavage toxicity study with a 13-week interim kill in which mice were dosed with FTC at dose levels of 0, 167, 500 or 1500 mg/kg/day. All doses were well

tolerated. There were no treatment related gross or histopathologic alterations. FTC was negative in a standard battery of genotoxicity assays. The pharmacokinetic characteristics of FTC were similar in mice and humans. The AUC values in the mouse study were: 77 (low), 231 (mid) and 678.5 microgram*hr/ml at the high dose. FTC is being administered once daily at a dose level of 200 mg/day (AUC_{ss} = 9.6 microgram*hr/ml). The sponsor has utilized the toxicokinetic endpoint (AUC) for the determination of the high dose that meets the criterion in the ICH Guideline regarding acceptability of 25 times exposure as being adequate. Thus, a dose level of 750 mg/kg/day in mice is expected to provide systemic exposures (339.25 microgram*hr/ml extrapolated from the high dose) approximately 35 times the human exposure. The low and mid doses were arithmetically determined, with the low and mid doses expected to provide approximately 3 and 10 times the human exposure, respectively.

Executive CAC Recommendations and Conclusions:

The Committee concurred with the sponsor's proposed doses of 0, 60, 200 or 600 for the rat carcinogenicity study provided that the exposure multiples anticipated are achieved in the carcinogenicity study. The committee noted that the proposed doses provided only slightly higher exposures over the 25-fold of the clinical exposures necessary for a valid study. If the clinical dose were to increase, the carcinogenicity study could be made invalid. Therefore, the committee suggests that the sponsor should consider increasing the dose to provide higher exposures since there were no toxicities seen in the rat study at doses up to 3000 mg/kg.

The Committee concurred with the sponsor's proposed doses of 0, 75, 250 or 750 for the mouse carcinogenicity study provided that the anticipated exposure multiples of the clinical exposure are achieved. The committee noted that the proposed doses provided only slightly higher exposures over the 25-fold of the clinical exposures necessary for a valid study and are interpolated values. If the clinical dose were to increase or the anticipated exposures were not achieved, the carcinogenicity study could be made invalid. Therefore, the committee suggests that the sponsor should consider increasing the dose to provide higher exposures since there were no toxicities seen in the mice study at doses up to 1500 mg/kg.

/s/

Joseph DeGeorge, Ph.D.
Chair, Executive CAC

cc:\

/Division File, HFD-530
/JFarrelly, HFD-530
/PVerma, HFD-530
/LStephens, HFD-530
/ASeifried, HFD-024

/s/

Joseph DeGeorge
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(b)(5) PRE-decisional



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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

RECORD OF INDUSTRY MEETING

Date of Meeting	June 5, 2001
IND	<input type="text"/>
Drug	Coviracil® (emtricitabine) Capsules
Indication	Treatment of HIV-1 infection
Sponsor	Triangle Pharmaceuticals
Type of Meeting	Drug Development Meeting

FDA Attendees

Debra B. Birnkrant, M.D., Acting Division Director, DAVDP
Therese Cvetkovich, M.D., Medical Team Leader, DAVDP
Russell Fleischer, PA-C, MPH, Senior Clinical Analyst, DAVDP
Joseph G. Toerner, M.D., Medical Officer, DAVDP
Kendall Marcus, M.D., Medical Officer, DAVDP
Sumati Nambiar, M.D., Medical Officer, DAVDP
James G. Farrelly, Ph.D., Pharmacology Team Leader, DAVDP
Priham Verma, Ph.D., Pharmacologist, DAVDP
Kellie S. Reynolds, Pharm.D., Pharmacokinetics Team Leader, DAVDP
George Lunn, Ph.D., Chemist, DAVDP
Lalji Mishra, Ph.D., Acting Microbiology Team Leader, DAVDP
Gregory Soon, Ph.D., Acting Statistical Team Leader, DAVDP
Tom Hammerstrom, Ph.D., Mathematical Statistician, DAVDP
David L. Roeder, M.S., Associate Director for Regulatory Affairs, ODEIV
Melissa Truffa, R.Ph., Regulatory Project Manager, DAVDP
Karen A. Young, RN, BSN, Regulatory Project Manager, DAVDP

Triangle Attendees

David W. Barry, M.D., Chairman and Chief Executive Officer

[redacted]
Michael Dalton, Ph.D., Director, Regulatory Affairs

John Hinkle, Ph.D., Senior Biostatistician

Anne McKay, Vice President, Regulatory Affairs

George Painter, Vice President, Research and Development

Joseph Quinn, MSPH, Vice President Biometrics

Frank Rousseau, M.D., Vice President Clinical Affairs and Chief Medical Officer

Thomas Shumaker, Associate Director, Regulatory Affairs

Charles Wakeford, Ph.D., Director, Biometrics

Consultants for Triangle

- /
- /
- Ian Sanne, MBBCH, FCB (SA), DTM&H, M.D., Director Clinical Trials Unit, Wits Health Consortium, Principal Investigator for Study FTC-302
- /

Background

Triangle provided a meeting background document dated March 30, 2001 (Serial Number 331) that included pre-clinical data and an overview of the clinical development of emtricitabine. The Sponsor requested a clinical development meeting with the Division with the following objectives: 1) to review the clinical development plan for emtricitabine, and 2) to determine if the Division is in agreement that the data provided will support the requirements for filing of a New Drug Application (NDA) for emtricitabine.

Discussion

Triangle began the meeting with a presentation of an overview of the resistance profile, clinical efficacy and safety data for emtricitabine (Please see presentation slides.) After the presentation, the Sponsor provided an update on their efforts to have the Medicines Control Council (MCC) of the Republic of South Africa reconsider their decision to terminate FTC-302. The Sponsor's proposed questions were then addressed.

FTC-302

Triangle recently submitted a written request to the MCC to reconsider their position on study FTC-302. The Sponsor is optimistic that the MCC will reverse their current opinion of the FTC-302 study and ultimately, the trial will be recognized as a well-controlled trial conducted under Good Clinical Practices. However, the Sponsor relayed that it may take several months before the MCC considers the request.

The Sponsor requested an opportunity to submit all the data from FTC-302 to the Division for our consideration.

In response, the Division stated that the Agency would not accept the FTC-302 study as a pivotal trial in support of an NDA unless the MCC reverses its decision and changes their current view of the study. Regardless of the outcome of the MCC decision, the Agency will review the data once an NDA is submitted, but believe it would not be appropriate to review these data prior to that time. Dr. Birnkrant quoted from a memo from Dr. David Lepay who referred to 21 CFR 312.12(c)(1) and 21 CFR 312.120(c)(2) as reasons why FTC-302 can not be considered a pivotal study.

The Sponsor will submit a document to the Division that supports their position on why the study should be considered adequate and well-controlled and a proposed timeline for submission of an NDA. The Division will provide feedback once the document is received and reviewed.

Pre-Clinical

1. Based on the [redacted] data summarized in the briefing document on page 11, do you agree that emtricitabine may be less likely to be associated with [redacted] than lamivudine?
2. What further data would be required to allow for this claim to be made in the labeling for Coviracil?

The Division believes the Sponsor has a very complete pre-clinical package. A claim that emtricitabine has [redacted] lamivudine would require data from a direct comparative clinical trial. Without such data, the Division would not include information about [redacted] in an emtricitabine label.

Virology

1. Is this data adequate to allow for this claim to be made in the labeling for the product? If no, what additional data or studies would be required to make this claim?
2. Do you agree that the in vitro and the in vivo resistance data summarized in the briefing document provide adequate evidence of the lower incidence of M184V mutations in patients treated with emtricitabine compared to lamivudine?

Virologic failure rates were nearly identical in the emtricitabine and lamivudine groups. In studies FTC-302 and 301, a claim that emtricitabine lowers the incidence of M184V mutations did not translate into improved clinical outcome. Therefore, additional resistance data would be necessary that correlate differences in resistance patterns with clinical outcomes. The Sponsor is encouraged to submit a plan to further investigate the resistance profile of emtricitabine.

Clinical

1. Do you agree that Coviracil does not have hepatotoxic potential?

2. **Do you agree that the overall database generated to date support the safety and efficacy of Coviracil?**
3. **Do you agree that the data support equivalence of a once-daily 200 mg Coviracil dose to a twice-daily 150 mg dose of Epivir®?**
4. **Does the overall safety and efficacy data support traditional approval of the drug? If not, what other data are required? If not, does the current database support accelerated approval of Coviracil? If yes, what phase 4 studies would be required to support traditional approval?**

It is not possible to state that FTC is without hepatotoxic potential. Should FTC ultimately receive approval, the adverse event profile will be described in the label to reflect the data that have been generated in clinical trials.

It is premature for us to agree that the database supports the safety and efficacy of emtricitabine or that emtricitabine is equivalent to lamivudine; these will be review issues.

At this time, the Division does not agree that there are sufficient data to support either the traditional or accelerated approval of emtricitabine. In general, the results from adequate and well-controlled studies must be submitted to support an application. As stated above, the Agency does not consider FTC-302 as a pivotal trial due to its termination by the MCC, unless and until such time that the MCC reverses its position. In addition, because of other problems that were identified (such as the very large number of protocol violations), FTC-302 may not meet the standard for studies that the Division uses to support a marketing application even if the MCC reverses its decision to close FTC-302.

Currently, the Division believes a standard review and traditional approval is more appropriate given the issues surrounding FTC-302. The Sponsor may make argument for accelerated approval and/or priority review at the time of NDA submission. An Advisory Committee meeting is likely to be necessary for this product and a standard review would provide necessary preparation time.

Summary/Action Items

1. The Sponsor will review the compliance data for FTC-301, 302, and 303.
2. The Sponsor will further explore wild type failures in emtricitabine. In addition, the Sponsor will phenotype all wild type failures.
3. The Sponsor will submit proposals for additional virologic research.
4. The Division will not independently review FTC-302 data prior to the submission of an NDA.
5. The Division will attempt to provide documentation of the opinion of the Senior Advisor for Science on the acceptance of study FTC-302 in an NDA for emtricitabine.
6. The Sponsor will submit a proposal that would support the use of FTC-302 as one of the proposals and provide comments in a timely fashion.

**RECORD OF INDUSTRY MEETING**

Date of Meeting: October 28, 1998

IND:

Drug: FTC Capsules

Indication: Treatment of HIV-1 Infection

Sponsor: Triangle Pharmaceuticals

Type of Meeting: Drug Development Meeting

FDA Attendees:

Heidi Jolson, M.D., M.P.H., Director, Division of Antiviral Drug Products
Debra Birnkrant, M.D., Deputy Director, Division of Antiviral Drug Products
Walla Dempsey, Ph.D., Assoc. Director, Division of Antiviral Drug Products
Stanka Kukich, M.D., Medical Team Leader
Russell Fleischer, PA-C, M.P.H., Clinical Reviewer
Tom Hammerstrom, Ph.D., Statistical Reviewer
Paul Flyer, Ph.D., Statistical Team Leader
Prabhu Rajagopalan, Ph.D., Pharmacokinetics Reviewer
Kelly Reynolds, Ph.D., Acting Pharmacokinetics Team Leader
Narayana Battula, Ph.D., Microbiology Reviewer
Lauren Iacono-Connors, Ph.D., Acting Microbiology Team Leader
Pete Verma, Ph.D., Pharmacology Reviewer
Jim Farrelly, Ph.D., Pharmacology Team Leader
George Lunn, Ph.D., Chemistry Reviewer
Joe Toerner, Ph.D., Medical Officer
Terrie Crescenzi, R.Ph., Regulatory Management Officer

External Constituents:

Walter Capone, Vice-President of Marketing
John Delehanty, Ph.D., Director of HBV Clinical Research and Project Leader for FTC
Anne McKay, Vice-President of Regulatory Affairs
Diego Maralles, M.D., Clinical research Physician
Joseph Quinn, Director of Biometrics
Franck Rousseau, M.D., Vice-President of Medical Affairs
George Szczech, D.V.M., Ph.D., Vice-President of Toxicology and Preclinical Pharmacology
Charles Wakeford, Ph.D., Associate Director of Biometrics
Laurene Wang, Ph.D., Associate Director of Clinical Pharmacology

Background:

The sponsor requested an end-of-phase 2 meeting to discuss the clinical development of FTC for the treatment of HIV-1 infection and to gain concurrence on the proposed contents of an NDA. At the beginning of the meeting Mr. Fleischer and Dr. Jolson indicated that it would be more appropriate for this meeting to focus on general drug development issues because the sponsor is very early in the drug development process. No agreements on the phase 3 development of FTC could be made at this time; however, the advice and discussions would be comparable to that in an end-of-phase 2 meeting. Scheduling of an official end-of-phase 2 meeting after additional data are generated on this product would provide another opportunity to discuss and reach closure on a phase 3 development plan.

Discussion:

1. With regard to the toxicology data, is it acceptable that the carcino-bioassay studies be conducted as a phase 4 commitment?

It is acceptable that the carcinogenicity studies for FTC for the treatment of HIV be conducted after an NDA has been filed, as a Phase IV commitment. However, the planned studies, in two species, should be started soon after the initiation of Phase III studies.

The Division requested that the sponsor submit for review any reports from the completed non-clinical safety studies. If final individual study reports are not available, an integrated summary report of toxicologic findings based on unaudited draft reports of the completed animal studies should be submitted. This is described in the document "Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-derived Products. This "Guidance for Industry" can be found at www.fda.gov/cder/guidance/index.htm. We request that you also submit a report of the six-month in-life results of the ongoing one-year study in cynomologus monkeys.

2. We expect the data generated from the clinical plan proposed herein will support a label claim for "Treatment of HIV-1 infection in adults _____" Do you agree that the enclosed package of data will qualify for accelerated approval?

a. Dose selection

The Division expressed numerous concerns about the utility of the current database from the two phase 1 studies as the basis for selection of the dose for the phase 3 studies and the risk to the sponsor associated with such a selection. Concerns were raised about the small number of subjects enrolled, the limited duration of dosing, and whether the data on reductions in HIV-1 RNA demonstrated meaningful differences among the doses studied in FTC-101 and 102. It was suggested that the sponsor conduct additional dose finding studies or modify the proposed clinical trials to include additional doses of FTC

for comparisons. The sponsor was encouraged to propose additional dose finding studies, taking into account trial design issues, practicality, and any ethical considerations associated with the conduct of such trials.

FDA also requested the opportunity to review the data from [redacted] in addition to the summaries provided in the background document.

b. Proposed Phase 3 Trial FTC-301.

The Division expressed several reservations about the design of FTC-301, an open-label comparison of FTC in combination with d4T once daily and nevirapine once daily vs. 3TC in combination d4T twice daily and nevirapine twice daily. Specifically the following issues were raised:

- The proposed trial is open label. The sponsor was referred to the recent experience with the Sustiva trial DMP-006, in which unequal dropout rate among arms was problematic.
- D4T and nevirapine have not been approved for once daily dosing. Thus, this dosing schedule would need to be approved before any approval of FTC in order to include the once daily dosing description in a label for FTC, otherwise d4T and nevirapine would be misbranded. In addition, a concern was expressed that once daily dosing with d4T and nevirapine may be sub-therapeutic even though it would represent a convenient dosing schedule. The Division recommended that additional trials be conducted to address practice of medicine issues.
- The rationale for 2 nucleosides plus 1 non-nucleoside was questioned. Although this is an acceptable regimen according to HHS guidelines, the combination may not provide durable suppression of HIV.
- Superiority to 3TC may not be shown if the trial were unable to demonstrate that 3TC in combination with d4T and nevirapine was effective. In addition, changing three drugs (dosing regimens of two drugs and addition of FTC) makes interpretation of any results difficult. For example, D4T and nevirapine once daily may have a better compliance rate than the approved dosing regimen for these drugs in the 3TC containing arm, and therefore, may be superior without the substitution with FTC for 3TC.
- Because of the complexity of the proposed study with multiple parameters, it will be difficult to assess the contribution of FTC in the proposed trial design.
- The sponsor was cautioned that if FTC-301 is submitted as part of an NDA package, and the trial doesn't demonstrate superiority, then the data can be used only to support the safety database.

c. Proposed Phase 3 Trial FTC-303

The Division expressed the following concerns about the design of FTC-303.

- The proposed trial is open label.
- The equivalence design of this trial is risky. Because it is unclear how much 3TC will contribute to the comparison arm, a smaller delta may be required. The sponsor was encouraged to document the contribution of 3TC to the proposed regimen when choosing delta.
- All patients should be followed until the last patient enrolled has reached 48 weeks.
- The sponsor was advised of the potential risk of using the [redacted] Ultrasensitive Assay for measurement of HIV copy number. Because the assay is not FDA approved, interpretation of the results may be problematic unless the sponsor is able to submit a comprehensive description of the performance characteristics of the proposed experimental assay.

- The primary analysis for virologic success should be at 24 weeks and 48 weeks, not 16 weeks and 48 weeks.
- The toxicity management program needs to be addressed.
- Clear criteria for handling failures must be developed.

The sponsor indicated that this trial has begun to enroll.

d. Γ

e. Proposed Trial FTC-ANRS

The rationale for this trial was discussed. The sponsor was informed that this open-label, short term, single arm study would not support a regulatory decision, except as part of the safety database. In addition, the sponsor was cautioned that this study would need to enroll an appropriate number of methadone patients in order to characterize any type of drug-drug interactions.

Additional Issues/Discussions:

1. The Division reiterated the fact that they could not concur with the proposed drug development plan at this point. The sponsor was encouraged to talk with the Division to plan the studies.
2. The Division offered the sponsor an opportunity to discuss their drug development plan at a closed session advisory committee meeting, particularly in light of the unusual design issues surrounding the development of FTC.

Action Items:

1. The Division agreed to provide the sponsor with written comments on the submitted protocols.

Minutes preparer: _____ Date: _____

Conference Chair: _____ Date: _____

Concurrence:

- HFD-530/Dir/Jolson-13Nov98
- HFD-530/DepDir/Birnkrant-16Nov98
- HFD-530/AssocDir/Dempsey-13Nov98
- HFD-530/MTL/Kukich-13Nov98
- HFD-530/CR/Fleischer-10Nov98
- HFD-530/Stat/Hammerstrom-12Nov98
- HFD-530/StatTL/Flyer-12Nov98
- HFD-530/Biopharm/Rajagopalan-16Nov98
- HFD-530/BiopharmTL/Reynolds-16Nov98
- HFD-530/Micro/Battula-13Nov98
- HFD-530/MicroTL/Connors-13Nov98
- HFD-530/Pharm/Verma-12Nov98
- HFD-530/PharmTL/Farrelly-12Nov98
- HFD-530/Chem/Lunn-16Nov98
- HFD-530/RMO/Crescenzi-9Nov98

Distribution:

- Original IND [redacted]
- Division file
- HFD-530

IND [redacted] serial #027/October 15, 1998

Meeting Minutes

REQUEST FOR CONSULTATION

Division/Office):

Janie Beam, DMETS

11FD-420, (Rm. 6-34, PKLN Bldg.)

FROM: Virginia L. Yoerg, Regulatory Health Project Manager
Division of Antiviral Drug Products, HFD-530

DATE May 1, 2003	IND NO.	NDA NO. 21-500	TYPE OF DOCUMENT Proposed labeling and tradename	DATE OF DOCUMENT April 28, 2003
NAME OF DRUG emtricitabine		PRIORITY CONSIDERATION Standard Review	CLASSIFICATION OF DRUG Treatment of HIV	DESIRED COMPLETION DATE June 16, 2003

NAME OF FIRM: Gilead Sciences

REASON FOR REQUEST

I. GENERAL

- | | | |
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| <input type="checkbox"/> NEW PROTOCOL
<input type="checkbox"/> PROGRESS REPORT
<input type="checkbox"/> NEW CORRESPONDENCE
<input type="checkbox"/> DRUG ADVERTISING
<input type="checkbox"/> ADVERSE REACTION REPORT
<input type="checkbox"/> MANUFACTURING CHANGE/ADDITION
<input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> PRE-NDA MEETING
<input type="checkbox"/> END OF PHASE II MEETING
<input type="checkbox"/> RESUBMISSION
<input type="checkbox"/> SAFETY/EFFICACY
<input type="checkbox"/> PAPER NDA
<input type="checkbox"/> CONTROL SUPPLEMENT | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER
<input type="checkbox"/> FINAL PRINTED LABELING
<input type="checkbox"/> LABELING REVISION
<input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE
<input type="checkbox"/> FORMULATIVE REVIEW
<input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): Trade name review |
|--|--|--|

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):	<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- | | |
|---|--|
| <input type="checkbox"/> DISSOLUTION
<input type="checkbox"/> BIOAVAILABILITY STUDIES
<input type="checkbox"/> PHASE IV STUDIES | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE
<input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS
<input type="checkbox"/> IN-VIVO WAIVER REQUEST |
|---|--|

IV. DRUG EXPERIENCE

- | | |
|--|---|
| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
<input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
<input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)
<input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
<input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE
<input type="checkbox"/> POISON RISK ANALYSIS |
|--|---|

V. SCIENTIFIC INVESTIGATIONS

<input type="checkbox"/> CLINICAL	<input type="checkbox"/> PRECLINICAL
-----------------------------------	--------------------------------------

COMMENTS, CONCERNS, and/or SPECIAL INSTRUCTIONS:

The NDA was submitted September 3, 2002, and DAVIDP would appreciate a tradename evaluation by June 16, 2003. The applicant had originally asked us to review "Coviracil" for the tradename, but no longer wants to use that name. Please review these two alternative names.

PDUFA DATE: July 3, 2003, Internal Action Date: July 2, 2003.

ATTACHMENTS: Draft Package Insert and draft carton and bottle labels

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> MAIL <input type="checkbox"/> HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Virginia Yoerg
5/1/03 02:23:57 PM

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information

NDA 21-500	Efficacy Supplement Type SE-	Supplement Number
Drug: Emtriva (emtricitabine) capsules		Applicant: Gilead Sciences, Inc.
RPM: Virginia L. Yoerg		HFD-530 Phone # (301) 827-2335
Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)		Reference Listed Drug (NDA #, Drug name): N/A
❖ Application Classifications:		
• Review priority		<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority
• Chem class (NDAs only)		Type 1
• Other (e.g., orphan, OTC)		Type AA (HIV)
❖ User Fee Goal Dates		July 3, 2003
❖ Special programs (indicate all that apply)		<input type="checkbox"/> None <input type="checkbox"/> Subpart H <input type="checkbox"/> 21 CFR 314.510 (accelerated approval) <input type="checkbox"/> 21 CFR 314.520 (restricted distribution) <input checked="" type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review
❖ User Fee Information		
• User Fee		<input type="checkbox"/> Paid
• User Fee waiver		<input checked="" type="checkbox"/> Small business <input type="checkbox"/> Public health <input type="checkbox"/> Barrier-to-Innovation <input type="checkbox"/> Other
• User Fee exception N/A		<input type="checkbox"/> Orphan designation <input type="checkbox"/> No-fee 505(b)(2) <input type="checkbox"/> Other
❖ Application Integrity Policy (AIP)		
• Applicant is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• This application is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• Exception for review (Center Director's memo)		N/A
• OC clearance for approval		N/A
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.		<input checked="" type="checkbox"/> Verified
❖ Patent		
• Information: Verify that patent information was submitted		<input checked="" type="checkbox"/> Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted		21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> I <input type="checkbox"/> II <input type="checkbox"/> III <input type="checkbox"/> IV
N/A, since only applicable to 505(b)(2)		21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).		<input type="checkbox"/> Verified N/A

Exclusivity (approvals only)	
<ul style="list-style-type: none"> Exclusivity summary 	Yes, sent to M. Holovac
<ul style="list-style-type: none"> Is there an existing orphan drug exclusivity protection for the active moiety for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of sameness for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification! 	() Yes, Application # _____ (✓) No
❖ Administrative Reviews (Project Manager, ADRA) (indicate date of each review)	N/A
General Information	
❖ Actions	
<ul style="list-style-type: none"> Proposed action 	(✓) AP () TA () AE () NA
<ul style="list-style-type: none"> Previous actions (specify type and date for each action taken) 	N/A
<ul style="list-style-type: none"> Status of advertising (approvals only) 	(✓) Materials requested in AP letter () Reviewed for Subpart H
❖ Public communications	
<ul style="list-style-type: none"> Press Office notified of action (approval only) 	(✓) Yes () Not applicable
<ul style="list-style-type: none"> Indicate what types (if any) of information dissemination are anticipated 	(✓) None () Press Release () Talk Paper () Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert)	
<ul style="list-style-type: none"> Division's proposed labeling (only if generated after latest applicant submission of labeling) 	N/A
<ul style="list-style-type: none"> Most recent applicant-proposed labeling 	✓
<ul style="list-style-type: none"> Original applicant-proposed labeling 	Not necessary
<ul style="list-style-type: none"> Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) 	✓
<ul style="list-style-type: none"> Other relevant labeling (e.g., most recent 3 in class, class labeling) 	N/A
❖ Labels (immediate container & carton labels)	
<ul style="list-style-type: none"> Division proposed (only if generated after latest applicant submission) 	N/A
<ul style="list-style-type: none"> Applicant proposed 	✓
<ul style="list-style-type: none"> Reviews 	See Chemistry_Review
❖ Post-marketing commitments	
<ul style="list-style-type: none"> Agency request for post-marketing commitments 	✓
<ul style="list-style-type: none"> Documentation of agreements relating to post-marketing commitments 	✓
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	✓
❖ Memoranda and Telecons	✓
❖ Minutes of Meetings	
<ul style="list-style-type: none"> EOP2 meeting- Clinical Development Meetings 	✓
<ul style="list-style-type: none"> Pre-NDA meeting 	✓ July 3, 2002
<ul style="list-style-type: none"> Pre-Approval Safety Conference 	✓ May 19, 2003
<ul style="list-style-type: none"> Other 	✓

Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	N/A
❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	N/A
Summary Application Review	
❖ Summary Reviews (Division Director, Medical Team Leader)	✓
Clinical Information	
❖ Clinical reviews	✓
❖ Microbiology (efficacy) review	✓
❖ Safety Update review	✓ See Medical Officer's review
❖ Pediatric Page (separate page for each indication addressing status of all age groups)	✓
❖ Demographic Worksheet (<i>NME approvals only</i>)	✓ See Medical Officer's review
❖ Statistical review	✓
❖ Biopharmaceutical review	✓
❖ Controlled Substance Staff review(s) and recommendation for scheduling	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	✓
• Bioequivalence studies	N/A
CMC Information	
❖ CMC review	✓
❖ Environmental Assessment	
• Categorical Exclusion	✓
• Review & FONSI	N/A
• Review & Environmental Impact Statement	See Chemistry Review
❖ Micro (validation of sterilization & product sterility) review	N/A
❖ Facilities inspection (provide EER report) See Chemistry Review	Date completed: 6/25/03 (✓) Acceptable () Withhold recommendation
❖ Methods validation PENDING	() Completed (✓) Requested () Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review, including referenced IND reviews	✓
❖ Nonclinical inspection review summary	N/A
❖ Statistical review of carcinogenicity studies	N/A
❖ CAC/ECAC report	✓

3/3/03 VLY

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/s/

Virginia Yoerg

7/2/03 12:39:28 PM

Redacted

8

pages of trade

secret and/or

confidential

commercial

information



Food and Drug Administration
Rockville MD 20857

**MEMORANDUM OF TELEPHONE FACSIMILE
CORRESPONDENCE**

Date: September 30, 2002

To: Anne McKay
Vice President
Drug Regulatory Affairs
Triangle Pharmaceuticals, Inc.

From: Nitin Patel, R.Ph., Regulatory Project Manager, HFD-530

Through: Steven Gitterman, M.D., Medical Team Leader, HFD-530
James G. Farrelly, Ph.D., Pharmacology Team Leader, HFD-530
Pritam Verma, Ph.D., Pharmacologist, HFD-530

NDA: _____
21-500 Coviracil® (emtricitabine) Capsules

Subject: Pharmacology comments/requests

The following Pharmacology requests addressing the issue of impurities, are being conveyed to you on behalf of the review team:

1. Please submit animal toxicology studies that were conducted on the impurities in the capsules _____
2. Please discuss the results of the toxicology studies in relation to the impurities present in the capsules _____
3. Please determine the safety factors for each impurity.

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/

Nitin Patel, R.Ph.
Regulatory Project Manager
Division of Antiviral Drug Products

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/s/

Nitin Patel

9/30/02 12:00:03 PM

CSO

Pharmacology comments/requests for _____ 21-500: Hard copy sign-off
Steven Gitterman - 9/30/02.

Pharmacology comments/requests for _____ 21-500: Hard copy sign-off
Steven Gitterman - 9/30/02.

Steven Gitterman

10/4/02 07:51:27 AM

MEDICAL OFFICER



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation IV

FACSIMILE TRANSMITTAL SHEET

DATE: November 4, 2002

To: Anne McKay	From: Nitin Patel, R.Ph., Regulatory Project Manager
Company: Triangle Pharmaceuticals	Division of Antiviral Drug Products
Fax number: 919-493-5925	Fax number: 301-827-2471
Phone number: 919-493-5980	Phone number: 301-827-2442
Subject: NDA 21-500 Request for information on the emergence of HIV resistance	

Total no. of pages including cover: 2

Comments:

Document to be mailed: YES NO

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Food and Drug Administration
Rockville MD 20857

**MEMORANDUM OF TELEPHONE FACSIMILE
CORRESPONDENCE**

Date: November 4, 2002

To: Anne McKay
Vice President
Drug Regulatory Affairs
Triangle Pharmaceuticals, Inc.

From: Nitin Patel, R.Ph., Regulatory Project Manager, HFD-530

Through: Steven Gitterman, M.D., Medical Team Leader, HFD-530
Julian J. O'Rear, Ph.D., Microbiology Team Leader, HFD-530
Narayana Battula, Ph.D., Microbiologist, HFD-530

NDA: 21-500 Coviracil® (emtricitabine) Capsules

Subject: Request for information on the emergence of HIV resistance

The Division is unable to locate data on the emergence of HIV resistance for the clinical studies that were submitted in your application. However, there was a summary statement on study FTC-101 and FTC-302 (Volume 3, page 60) without supporting data. In Phase 3 clinical protocols FTC-301, 302 and 303, you stated that both phenotypic and genotypic resistance would be carried out at baseline, weeks 24 and 48. Additionally, viral genotyping would be carried out to determine the time to virologic failure as well as the proportion of patients in the different treatment arms who are virologic failures. The following request is being conveyed to you on behalf of the review team:

To facilitate the review of NDA 21-500, please provide the resistance data as a separate submission with copies to the clinical, statistical and microbiology reviewers.

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.

151

Nitin Patel, R.Ph.
Regulatory Project Manager
Division of Antiviral Drug Products

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/s/

Nitin Patel

11/6/02 09:32:13 AM

CSO

NDA 21-500, request for information on the emergence of
HIV resistance: Hard copy sign-off by Melisse Baylor
for Steven Gitterman - 11/4/02.

NDA 21-500, request for information on the emergence of
HIV resistance: Hard copy sign-off by Melisse Baylor
for Steven Gitterman - 11/4/02.

Steven Gitterman

11/7/02 01:24:26 PM

MEDICAL OFFICER



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation IV

FACSIMILE TRANSMITTAL SHEET

DATE: December 20, 2002

To: Anne McKay	From: Nitin Patel, R.Ph., Regulatory Project Manager
Company: Triangle Pharmaceuticals	Division of Antiviral Drug Products
Fax number: 919-493-5925	Fax number: 301-827-2471
Phone number: 919-493-5980	Phone number: 301-827-2442
Subject: NDA 21-500 Chemistry comments	
Total no. of pages including cover: 4	

Comments:

Document to be mailed: YES NO

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**MEMORANDUM OF TELEPHONE FACSIMILE
CORRESPONDENCE**

Date: December 20, 2002

To: Anne McKay
Vice President
Drug Regulatory Affairs
Triangle Pharmaceuticals, Inc.

From: Nitin Patel, R.Ph., Regulatory Project Manager, HFD-530

Through: Stephen P. Miller, Ph.D., Chemistry Team Leader, HFD-530
George Lunn, Ph.D., Chemist, HFD-530

NDA: 21-500

Drug: Coviracil® (emtricitabine) Capsules

Subject: Chemistry comments

The following comments are being conveyed on behalf of Stephen P. Miller, Ph.D., Chemistry Team Leader, and George Lunn, Ph.D., Chemist:

1. _____ is acceptable as a starting material for the drug substance. Please describe in detail the analytical methods used for this compound and summarize the validation results. Please consider designating a compound other than _____ as a starting material. We recommend that you select a candidate starting material that is separated from the final intermediate _____ by several reaction steps that include significant _____ procedures. Additionally, we believe that starting materials should have sufficiently simple structures such that routine testing procedures (_____) can assure identity. Please refer to the FDA fax dated 6/25/02, sent in connection with the emtricitabine IND _____.
2. Please provide a process description for the manufacture of the drug substance (currently at Vol. 3.2, pp. 46-57) that has typical quantities and times.
3. _____ Please indicate if you have any comparative solubility data on the polymorphs.

4. Please consider reducing the acceptance criteria for: _____ in the drug substance to _____% based on manufacturing capability as shown by representative batches.
5. We note that the _____ method for emtricitabine drug substance (STM 0531500, Vol. 3.3, p. 59) is virtually identical to the _____ method for the step 2 product (Method STM 0424000, Vol. 3.2, p. 108), only the _____ wavelength being different. However, with the _____ method retention times for _____-FTC and _____-FTC are _____ and _____ minutes, respectively, with the emtricitabine method the retention times are _____ and _____ minutes, respectively, an apparent inversion of elution order. Please comment on this apparent contradiction.
6. Please describe how the enantiomer of emtricitabine (TP-0274) is toxicologically qualified and please consider reducing the acceptance criterion for this compound in the drug substance specifications.
7. You state that the bags for drug substance storage are made of food grade approved material. Please provide reference to specific manufacturers or brands to identify the bags and to DMFs or CFR food contact regulations to support their use as drug substance packaging materials.
8. In connection with the drug substance stability data (Vol. 3.3, pp. 234-250) please confirm that methods 0531406, 0531405, 0531401, 0531402, 0531403, and 0531404 are subsets of method 0531400 and that this is the method described at Vol. 3.3, pp. 61-63 and validated at Vol. 3.3, pp. 93-154 for the specified impurities _____ and the unspecified impurities _____. So that we can compare the stability data please describe the methods T001-B, T001-C, and T001-D and show that they are validated for the specified impurities and, preferably, for the unspecified impurities also.
9. The _____ purity of the drug substance was measured for 3 batches at the initial time point and after storage at 25°C/60% RH for 12 months. Please consider extending this monitoring through at least 24 months for these 3 batches.
10. Please consider monitoring the products of inversion at _____ on stability (for the drug substance and drug product).
11. Please clarify where the final biostudy batch of capsules (70-035-4Q) was manufactured.
12. Please supply the actual artwork of the final bottle label and container carton (if applicable).
13. Batch TP-0006-00207 of the drug product appears to be exhibiting slower dissolution as it ages. Please provide individual dissolution values for this batch on stability. Have S2 or Tier 2 testing been required yet? Why does this batch appear to differ from the other batches?
14. Please indicate the criterion for going to Tier 2 testing in the dissolution method. Is it failure at S1, S2, or S3?

15. Please state if a stability update is expected during the review cycle. If so, when could we expect to receive it?
16. In the Methods Validation package (Volume 3.7) the list of samples to be supplied to the FDA laboratory contains emtricitabine drug substance validation batch, emtricitabine drug substance reference standard, and emtricitabine 200 mg capsules. Please add the specified impurities _____ to this list, if possible.

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/

Nitin Patel, R.Ph.
Regulatory Project Manager
Division of Antiviral Drug Products

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/s/

Nitin Patel

12/23/02 09:29:01 AM

CSO

Chemistry comments; NDA 21-500 Coviracil: Hard copy sign-off by
Stephen Miller - 12/20/02.

Chemistry comments; NDA 21-500 Coviracil: Hard copy sign-off by
Stephen Miller - 12/20/02.

Stephen Paul Miller

12/24/02 12:31:08 PM

CHEMIST



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation IV

FACSIMILE TRANSMITTAL SHEET

DATE: March 12, 2003

To: Martine Kraus, Ph.D., Director, Regulatory Affairs	From: Virginia L. Yoerg, Regulatory Health Project Manager
Company: Gillead Sciences, Inc.	Division of Antiviral Drug Products
Fax number: 650-522-5489	Fax number: 301-827-2523
Phone number: 650-522-5722	Phone number: 301-827-2335
Subject: NDA 21-500 Request for microbiology information	

Total no. of pages including cover: 3

Comments:

Document to be mailed: YES NO

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**MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE**

Date: March 12, 2003

To: Martine Kraus
333 Lakeside Drive
Foster City, CA 94404

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

Through: Debra Birnkrant, M.D., Division Director, HFD-530
Steven Gitterman, M.D., Ph.D., Medical Team Leader, HFD-530
Russ Fleischer, PA-C, MPH, Medical Reviewer, HFD-530
Julian J. O'Rear, Ph.D., Microbiology Team Leader, HFD-530
Narayana Battula, Ph.D., Microbiologist, HFD-530

NDA: 21-500 Coviracil® (emtricitabine) Capsules

Subject: Request for microbiology information

This fax is in follow up to the DAVDP's prior request of November 4, 2002, in which we requested that Triangle Pharmaceuticals provide resistance data sets for clinical studies FTC-301A and FTC-303. To complete the review of the NDA 21-500 for Coviracil®, it is essential that you provide the information requested herein. Failure to submit these data in a complete and reviewable format may impact regulatory action on your application.

Please submit the following data for studies FTC-301A and FTC-303. In addition, you may also provide FTC resistance data from early clinical trials or other clinical studies. You may utilize the table format provided below or another format that includes all of the elements listed.

1. The baseline genotype of individual patient's viral reverse transcriptase and protease genes
2. The phenotypic susceptibility to the test drugs at baseline
3. The changes in the phenotype and genotype at defined time points during the course of the study, such as Week 24 and Week 48.
4. The viral loads at baseline
5. The time of virologic failure
6. The viral RNA load at the time of virologic failure
7. The phenotype and genotype at the time of virologic failure
8. Resistance conferring mutations to the test drug or the drug class
9. Any additional information that helps in the evaluation of Coviracil

In addition, please submit the following information:

1. Individual patient data sets on phenotypic and genotypic resistance for studies FTC-301A and FTC-303 with changes in drug susceptibility and a list of all mutations at baseline week 24, 48 and at the time of virologic failure.
2. A summary of the resistance data for studies FTC-301A and FTC-303.
3. Identification of the central laboratories where the resistance analyses were conducted and the location of stored documents that contain the resistance data sets.

Please submit the amendment, in triplicate, no later than March 25, 2003.

Suggested tables format for presenting susceptibility/resistant data sets:

Table 1.

Patient ID	Treatment Group	RT Sequence at baseline	Change in RT seq at Wk 24/48	Phenotypic susc. at BL	Phenotypic susc. at Wk 24/48	RT mut at BL	RT mut at Wk 24/48	Drug/class related mutations	Other Info
------------	-----------------	-------------------------	------------------------------	------------------------	------------------------------	--------------	--------------------	------------------------------	------------

A Table similar to Table 1 will suffice for presenting protease susceptibility/resistance data sets.

To provide resistance data sets for virologic failures, please use the format in Table 2.

Table 2.

Patient ID	Treatment Group	Baseline viral load	Viral load at failure	Time to failure	RT genotype at baseline	RT genotype at failure	PR genotype at baseline	PR genotype at failure	Change in phenotype	Resistance conferring mutations	Other Info
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Virginia L. Yoerg
Regulatory Health Project Manager
Division of Antiviral Drug Products

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/s/

Virginia Yoerg
3/12/03 10:24:29 AM
CSO

hard copy signed and sent. Signed off by Birnkrant.

Steven Gitterman
3/12/03 04:07:24 PM
MEDICAL OFFICER



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation IV

FACSIMILE TRANSMITTAL SHEET

DATE: March 18, 2003

To: Martine Kraus, Ph.D., Director, Regulatory Affairs	From: Virginia L. Yoerg, Regulatory Health Project Manager
Company: Gilead Sciences, Inc.	Division of Antiviral Drug Products
Fax number: 650-522-5489	Fax number: 301-827-2523
Phone number: 650-522-5722	Phone number: 301-827-2335
Subject: NDA 21-500 Request for statistical information	
Total no. of pages including cover: 4	

Comments:

Document to be mailed: YES NO

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**MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE**

Date: March 18, 2003

To: Martine Kraus
333 Lakeside Drive
Foster City, CA 94404

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

Through: Debra Birnkrant, M.D., Division Director, HFD-530
Steven Gitterman, M.D., Ph.D., Medical Team Leader, HFD-530
Russ Fleischer, PA-C, MPH, Medical Reviewer, HFD-530
Greg Soon, Ph.D., Statistics Team Leader, HFD-530
Susan Zhou, Ph.D., Statistics Reviewer, HFD-530

NDA: 21-500 Coviracil® (emtricitabine) Capsules

Subject: Request for statistical information

The following questions are being conveyed on behalf of Susan Zhou, Ph.D., regarding Study FTC-301A, as submitted in NDA 21-500, received September 3, 2002. If you have any questions, feel free to contact us.

A. Status of Patients in Week 48 Population

1. Please report subject's censorship in the Week 48 population as of the cutoff date October 24, 2002. Please summarize patterns of missing data including censoring by treatment arm as described in the protocol (Vol. 5.58, Section 6.5 Handling of Missing Data and Censoring). We suggest that you determine whether a patient completed Week 48 or not using last date on study drug and last date of HIV viral load measurement.
2. Regarding status of subjects on d4T and FTC at Week 48, please create variables to indicate the last date on FTC and d4T respectively. Variables for censorship should also be created.

B. Drug Administration Data Set *drugad.xpt*

3. In the SAS transport file *drugad*, there are substantial missing values regarding study drug at baseline (D0), i.e., missing in 'drug', 'bottle', 'stdt', 'stdt_' etc. Many subjects in 'Stavudine' (trt='C') arm had only Emtricitabine information but no 'Stavudine' information. Conversely, many subjects in 'Emtricitabine' (trt='D') arm had no baseline info for taking Emtricitabine. Please provide your explanation for these discrepancies.

4. Please perform analysis on the drug information data sets and create a new data set, which includes the following variables:
 - 1) Number of Randomization
 - 2) Treatment group
 - 3) First date on study drug d4T or placebo d4T
 - 4) First date on study drug FTC or placebo FTC
 - 5) Last date on study drug d4T or placebo d4T and a flag for censorship
 - 6) Last date on study drug FTC or placebo FTC and a flag for censorship
 - 7) Total number of days on FTC or placebo PTC through Week 48
 - 8) Total number of days on d4T or placebo d4T through Week 48
 - 9) Flag for switching study drugs, i.e., from FTC to d4T and vice versa
 - 10) First date of switching

Some of the variables will be useful to define the status of patients in the Week 48 ITT population.

C. Adjusted Exposure Days of d4T and FTC

5. Two variables *expad4T* and *expaFTC* were created by a SAS program *adher301a.sas*, indicating the adjusted exposure days of d4T or FTC, respectively.
 - It appears that these variables are not actual exposure days of study drugs. They share the same value as 'study days' (=studydt-bldate+1) for each subject. If a subject was not permanently discontinued from the study, it appears that the last date of lab measurement for 'studydt' was assigned. The baseline date 'bldate' was created combining the first date of d4T or FTC, or lab date if the first date of d4T/FTC is missing, etc.
 - Only a fraction of study participants had same exposure days of d4T and FTC, according to data set *drugad*. Therefore, assuming that a subject should have the same exposure days of d4T (d4T placebo) or FTC (or FTC placebo) is not valid.

Please submit revised SAS programs and provide appropriate information regarding exposure days of d4T and FTC.

D. Other Data Problems

6. The last date of HIV-1 RNA measurement (*hiv_dt*) and *hiv_day* you created has some discrepancies with information in *surmark.xpt*. Please verify your SAS program *disp301a.sas*.
7. Some of the *SAS XPT* files were not clean and modifications of individual data were present in many *SAS* programs. Modifications of individual data were observed on variables such as *drug*, *stdt_*, *spdt_*, *randnum*, *Study_dt*, *studyday*, *hv4850I* and *hv48400I*, etc. It is difficult for us to accept the modification and reclassification of virologic failure status in a *SAS* program, even if the reclassifications were concurred with investigators. Please assess and remedy these data problems and provide cleaned new copies of *SAS XPT* files.