

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-500

Correspondence

MAY 8 2002

Food and Drug Administration
Rockville MD 20857

Thomas K. Shumaker
Associate Director, Drug Regulatory Affairs
Triangle Pharmaceuticals
4611 University Drive
P.O. Box 50530
Durham, NC 27717-0530

RE: Triangle Pharmaceuticals, Small Business Waiver Request 2002.020 for Coviracil (emtricitabine).

Dear Mr. Shumaker:

This responds to your March 21, 2002, letter requesting a waiver of the human drug application fee for the new drug application (NDA) for Coviracil (emtricitabine) under the small business waiver provision of section 736(d)(1)(E)¹ of the Federal Food, Drug, and Cosmetic Act (the Act) (Waiver Request 2002.020). For the reasons described below, the Food and Drug Administration (FDA) grants the request from Triangle Pharmaceuticals, Inc. (Triangle) for a small business waiver of the application fee for Coviracil (emtricitabine).

According to your waiver request, Triangle is a small business with _____ s including its affiliates. You note that Triangle was approved previously for a small business waiver on October 29, 1999, for submission of the _____. You note that the submission was delayed beyond the time limit specified in the waiver (June 23, 2000) and that Triangle has since discontinued development of this compound. You now request that the user fee waiver refer to the pending NDA submission for _____. You state that Triangle anticipates submitting this new NDA by _____.

You also acknowledge one wholly-owned affiliate, Antiviral Development Corporation (AVID), which has no employees.

Under the Act, a waiver of the application fee shall be granted to a small business for the first human drug application that a small business or its affiliate² submits to the FDA for review. The small business waiver provision entitles a qualified small business to a waiver when the business meets the following criteria: (1) a business must employ fewer than 500 persons, including employees of its affiliates, and (2) the marketing application must be the first human drug application, within the meaning of the Act, that a company or its affiliate submits to FDA.

¹ 21 U.S.C. 379h(d)(1)(E).

² "The term 'affiliate' means a business entity that has a relationship with a second business entity if, directly or indirectly — (A) one business entity controls, or has the power to control, the other business entity; or (B) a third party controls, or has the power to control, both of the business entities" (21 U.S.C. 379g(9)).

FDA's decision to grant Triangle's request for transfer of the small business waiver for (emtricitabine) is based on the following findings. First, the Small Business Administration (SBA) determined and stated in its letter dated April 15, 2002, that Triangle has fewer than 500 employees, including those of its affiliates, AVID. Second, according to FDA records, the marketing application for Coviracil will be the first human drug application, within the meaning of the Act, to be submitted to FDA by Triangle or its affiliates. Consequently, your request that the small business waiver of the application fee _____ be transferred to _____ for Coviracil (emtricitabine) is granted provided FDA receives the marketing application for _____ no later than April 14, 2003, 1 year after the effective date of the size determination made by SBA. This decision effectively cancels the original small business waiver for the application fee for _____ (Waiver Request 99.046).

FDA records show that Triangle's _____ has not yet been submitted to FDA. Please include a copy of this letter with your application when it is submitted. If FDA refuses to file the application or Triangle withdraws the application before it is filed by FDA, a reevaluation of the waiver may be required should the company resubmit its marketing application. If this situation occurs, Triangle should contact this office approximately 90 days before it expects to resubmit its marketing application to determine whether it continues to qualify for a waiver.

FDA plans to disclose to the public information about its actions granting or denying waivers and reductions. This disclosure will be consistent with the laws and regulations governing the disclosure of confidential commercial or financial information.

If any billing questions arise concerning the marketing application or if you have any questions about this small business waiver, please contact Beverly Friedman or Michael Jones at 301-594-2041.

Sincerely,

/s/
Jane A. Axelrad
Associate Director for Policy
Center for Drug Evaluation and Research



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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

IND

Triangle Pharmaceuticals, Inc.
Attention: Anne McKay
Vice President, Drug Regulatory Affairs
4 University Place
4611 University Drive
Durham, NC 27707

Dear Ms. McKay:

Please refer to the meeting between representatives of your firm and FDA on June 5, 2001. The purpose of this drug development meeting was to discuss development plans for Coviracil® (emtricitabine) Capsules for treatment of HIV infected patients.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please contact Ms. Karen Young, Regulatory Health Project Manager, at (301) 827-2335.

Sincerely yours,

Anthony W. DeCicco, R.Ph.
Supervisory Consumer Safety Officer
Division of Antiviral Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Attachment



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND

Triangle Pharmaceuticals
Attention: Anne McKay
Vice President, Drug Regulatory Affairs
4 University Place
4611 University Drive
Durham, North Carolina 27707

Dear Ms. McKay:

Please refer to the meeting between representatives of your firm and FDA on July 3, 2002. The purpose of this pre-NDA meeting was to answer your questions and provide comments on your proposals pertaining to the planned NDA submission of Coviracil® (emtricitabine) for the treatment of HIV-1 infection.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Nitin Patel, Regulatory Project Manager, at 301-827-2335.

Sincerely, _____

{See appended electronic signature page}

Anthony W. DeCicco, R.Ph.
Chief, Project Management Staff
Division of Antiviral Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Attachment



IND

Triangle Pharmaceuticals, Inc.
Attention: Ms. Anne McKay
Vice President, Drug Regulatory Affairs
4 University Place, 4611 University Drive
Durham, NC 27707

Dear Ms. McKay:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Coviracil™ (emtricitabine) Capsules. We refer you to the clinical hold letters of April 12, 2000, and February 14, 2001, meetings of January 12, 2000, April 18, 2001 and June 5, 2001, and to correspondence between Triangle and the Medicines Control Council (MCC) of the Republic of South Africa between January 2000 and August 2001.

We also refer to your amendment dated July 13, 2001 (serial # 370), containing a legal brief prepared by _____

The above materials have been extensively reviewed by the Agency. Our conclusion is that study FTC-302 can not serve as a pivotal efficacy trial in a New Drug Application for Coviracil. The Agency placed study FTC-302 on clinical hold in April 2000 (see clinical hold letter of April 12, 2000). Although you subsequently completed FTC-302, you never met the conditions for lifting the clinical hold, as outlined in FDA's April 12, 2000, and February 14, 2001, letters. Therefore, FTC-302 was conducted without a valid IND and the acceptance of the clinical data from that trial is governed by 21 C.F.R. § 312.120, "Foreign clinical studies not conducted under an IND." Based on the correspondence between Triangle and the MCC, FDA does not believe that FTC-302 meets all of the requirements in § 312.120, specifically § 312.120(c), which states that the research is required to have been conducted "in accordance with the ethical principles stated in the 'Declaration of Helsinki' [as set forth in § 312.120(c)(4),] or the laws and regulations of the country in which the research was conducted."



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

If you have any questions, please call Karen Young, Regulatory Project Manager, at 301-827-2335.

Sincerely, */S/*

{See appended electronic signature page}

Debra B. Birmkrant, M.D.
Division Director
Division of Antiviral Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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/s/

Debra Birnkrant
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IND

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secret and/or

confidential

commercial

information



NDA 21-500

Triangle Pharmaceuticals, Inc.
Attention: Anne McKay
Vice President, Drug Regulatory Affairs
4 University Place
4611 University Drive
Durham, NC 27707

Dear Ms. McKay:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Coviracil® (emtricitabine) Oral Capsule 200 mg

Review Priority Classification: Standard (S)

Date of Application: September 3, 2002

Date of Receipt: September 3, 2002

Our Reference Number: NDA 21-500

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on November 2, 2002 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be July 3, 2003.

Under 21 CFR 314.102(c), you may request an informal conference with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the ultimate approvability of the application. Alternatively, you may choose to receive a report by telephone.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Address all communications concerning this NDA as follows:

NDA 21-500

Page 2

U.S. Postal Service:

Center for Drug Evaluation and Research
Division of Antiviral Drug Products, HFD-530
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Antiviral Drug Products, HFD-530
Attention: Division Document Room N115
9201 Corporate Boulevard
Rockville, Maryland 20850-3202

If you have any questions, call Nitin Patel, R.Ph., Regulatory Project Manager, at (301) 827-2335.

Sincerely,

(See appended electronic signature page)

Debra Birnkrant, M.D.
Director
Division of Antiviral Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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/s/

Debra Birnkrant
11/18/02 01:43:10 PM



NO FILING ISSUES IDENTIFIED

NDA 21-500

Triangle Pharmaceuticals, Inc.
Attention: Anne McKay
Vice President, Drug Regulatory Affairs
4 University Place
4611 University Drive
Durham, NC 27707

Dear Ms. McKay:

Please refer to your September 3, 2002 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Coviracil® (emtricitabine) Oral Capsule 200 mg.

We also refer to your submissions dated July 22, 2002, July 30, 2002, and August 20, 2002.

We have completed our filing review of your application. At this time, we have not identified any potential review issues. Our filing review is only a preliminary review and deficiencies may be identified during substantive review of your application.

If you have any questions, call Nitin Patel, R.Ph., Regulatory Project Manager, at (301) 827-2335.

Sincerely,

{See appended electronic signature page}

Debra Birnkrant, M.D.
Director
Division of Antiviral Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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

/s/

Debra Birnkrant
12/2/02 09:35:23 AM
NDA 21-500



Food and Drug Administration
Rockville, MD 20857

IND [redacted]

**CERTIFIED MAIL
RETURN RECEIPT REQUESTED**

Triangle Pharmaceuticals
Attention: Anne McKay
Vice President, Drug Regulatory Affairs
4 University Place
4611 University Drive
Durham, North Carolina 27707
U.S.A.

Dear Ms. McKay:

Please refer to your Investigational New Drug Application (IND) submitted August 20, 1997, under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Coviracil (emtricitabine) Capsules.

We also refer to your submission, titled a complete response, dated January 15, 2001 (serial number 294), and received on January 16, 2001. Your submission provided a response to our April 12, 2000 letter, which cited the reasons that IND [redacted] was placed on partial clinical hold because of the medical risks identified in Study FTC-302, "A Randomized, Double Blind Equivalence Trial Comparing Emtricitabine to Lamivudine with Triple Combination in Antiretroviral-Drug Naïve HIV-1 Infected Patients". Our letter also outlined the information necessary to have the partial clinical hold removed.

WE HAVE COMPLETED OUR REVIEW OF YOUR RESPONSE AND CONCLUDE THAT REMOVAL OF THE PARTIAL CLINICAL HOLD IS NOT WARRANTED.

The following requirements, as outlined in our partial hold letter, were not adequately addressed in your response. Please note that the requirements for removal of the partial clinical hold appear in bold font and our responses to your submitted information appear in regular font.

1. Documentation of an MCC decision to allow the study to continue

Study FTC-302 was terminated by the Medicines Control Council of South Africa (MCC) on April 6, 2000 because of numerous and serious protocol violations which compromised the scientific integrity of the study. Since the MCC has not reversed their decision to terminate Study FTC-302, we conclude that the stipulation to document the MCC's decision to allow Study FTC-302 to continue was not met. Since there is no longer an opportunity for this decision to be reversed, based on the final decision of the MCC, we conclude that this requirement for resolution of the partial clinical hold cannot be met.

2. Satisfactory inspection of the clinical trial sites audited by the MCC and the FDA, along with resolution of any unacceptable findings

[redacted] an independent consulting group specializing in Good Clinical Practice audits and evaluations, as described in your complete response, identified two sites that exhibited a number of significant deficiencies. In addition, deviations from acceptable standards were identified in the following areas:

- the process and documentation of Informed Consent;
- enrollment of several unsuitable subjects;
- discrepancies in compliance and drug accountability;
- unacceptable management and reporting of Serious Adverse Events in several instances; and
- backlogs of CRF reviews that were "insufficient to maintain currency with study data and developments."

Documentation of how the aforementioned deviations were resolved was not provided in your submission. Therefore, the requirement for resolution of the partial clinical hold was not met.

3. Establishment of an independent data safety monitoring board (DSMB).

We do not view the establishment of a Clinical Steering Committee (CSC) to be an adequate response to our request that you establish an independent DSMB. The CSC included both Triangle employees and the principal investigator of the study, which called into question the independence of your committee. Therefore, because you did not establish an independent DSMB, this requirement for resolution of the partial clinical hold was not met.

Summarized below is the information needed to resolve these deficiencies.

Since Study FTC-302 was terminated by the MCC, it will not be possible for you to submit a response that would address our request for documentation of an MCC decision to allow the study to continue. Therefore, the partial clinical hold placed on IND [redacted] remains in effect. Finally, it is the recommendation of the Division of Antiviral Drug Products that you withdraw Study FTC-302.

Correspondence to this IND can be sent to either of the following addresses:

U.S. Postal Service:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Antiviral Drug Products, HFD-530
Attention: Division Document Room, N115
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Antiviral Drug Products, HFD-530
Attention: Division Document Room, N115
9201 Corporate Blvd.
Rockville, Maryland 20850

You may appeal the clinical hold decision to the Director, Office of Drug Evaluation IV at any time. However, please note that our procedures specify that review by the Office Director is automatic for continuance of a clinical hold.

If you have any questions, call Leslie Stephens, RN, MSN, Regulatory Project Manager, at 301-827-2335.

Sincerely,

{See appended electronic signature page}

Debra Birnkrant, M.D.
Acting Director
Division of Antiviral Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

/s/

Debra Birnkrant
2/14/01 03:18:04 PM
IND



JIE REGISTRATEUR VAN MEDISYNE
DEPARTEMENT VAN GESONDHEID
PRIVAATSAK X828
PRETORIA
0001

Teleks:
Telex:
Telefoon:
Telephone: (012) 312-0000
Faks:
Fax: (012) 328-4344

THE REGISTRAR OF MEDICINES
DEPARTMENT OF HEALTH
PRIVATE BAG X828
PRETORIA
0001

Navras • Inquiries:
Verwysing • Reference:

Medical Director

Pretoria

Fax: 012 664 223

Dear Dr: _____

January 31, 2000

Re: Adverse Events reported with the Study FTC 302.

I note with concern the reports of deaths associated with the FTC302 Trial. I also understand that there have been meetings of Investigators together with the company in both the US, and in South Africa, to discuss these events and the future plans for the study. I have discussed the situation with senior colleagues in the MCC and we would request the following:

- That the details of all deaths of patients that have occurred in this study, whether here or elsewhere, be forwarded to the MCC within the next 24 hours.
- That information regarding the action taken by the company with respect to informing the relevant Ethics Committees in South Africa about the reported deaths be forwarded to the MCC within the next 24 hours.
- ① ▪ That the discussions and recommendations of the two meetings held in the US and in South Africa be forwarded to the MCC within the next 24 hours.
- That all the relevant toxicological data pertaining to the study be forwarded to the MCC within 24 hours.

The MCC is sufficiently concerned about these reports to request that you stop recruiting for the study forthwith, until the data submitted by yourselves has been evaluated by the MCC, and a decision about whether the trial will be allowed to continue or not has been taken. I would also request that all correspondence and data that has been submitted to the FDA with respect to these deaths be similarly submitted to the MCC within 24 hours. As the monitoring CRO for this study, I understand that you may need to convey this message to the Triangle Company in the US to assist you in the provision of all the required information to the MCC.

I would further request that you convey to Triangle the MCC's concern that no formal approach about this matter has been initiated by the company despite the fact that they have been in contact with the FDA on this serious matter.

Please do not hesitate to phone Mrs. Matsosa or myself if you have any questions with regard to the above.

Yours sincerely

Helen Rees

Dr Helen Rees
CHAIRPERSON

From: Mike Dalton
To: Anne McKay; Claude Drobnes; Diego Miralles; Frank Rousseau; Jill Buckley; John Delehanty; Joseph Quinn; Susan Warwick
Date: 2/3/00 12:28PM
Subject: Contact with Dr. Helen Rees, Head of MCC

I spoke with Dr. Rees this AM regarding FTC-302. I offered to arrange a conference call with her which would include members from our clinical and safety team but she preferred to delay a broader discussion until the MCC had a chance to review the package of information we have provided (information presented at FDA meeting, safety update for all FTC trials, and recent package sent to FDA with our rationale for continuing study and measures taken to ensure patient safety) The key points made by Dr. Rees are the following:

- The MCC should have been contacted by Triangle sooner. Why were we talking to the FDA and not the MCC when this trial is being conducted in SA.
- The MCC is concerned about the manner in which this study is being conducted. She specifically mentioned that some patients with elevated LFTs were allowed to continue on study drugs (I think she heard this from the FDA). They are in the process of reviewing the information we provided to determine if the study should be continued. Dr. Rees has communicated to the CRO that, pending their review of the situation, no additional patients should be entered into FTC-302.
- The MCC is unable to find the safety reports that the CRO indicates they have submitted. When they requested information from the CRO, what they received was a brief summary that Dr. Rees said was inadequate. I subsequently discussed this point with the _____ and he reassured me that all SAEs have been submitted to the MCC and, if necessary, he will resubmit these to the MCC along with original cover letter.
- Dr. Rees asked who is the PI for the study (I told her I would have to check and follow-up with her). She went on to say that one of the investigators should be designated as the PI. The PI is responsible for monitoring the overall conduct of the trial and would be a contact person for the MCC regarding any safety issues. She stressed that the PI is not a role for the CRO.
- Dr. Rees said _____ conducting in SA

She viewed this as not living up to our initial commitment which was very bad press for Triangle and at least to one EC, unacceptable. I indicated I didn't know about this but would get the details and get back in touch with her.

During our conversation, I tried to address her questions and clarify areas of confusion. I explained the sequence of events with the FDA and that initially we provided the same info to both the FDA and the MCC and the FDA requested a meeting with us. During the meeting we told the FDA we had notified the MCC and EC about the events but had not yet heard back from them.

I indicated that we were willing to meet with Dr. Rees and her staff at their convenience and added that a meeting would probably be very useful. She said she would get back to us when they had completed their review or if she had any questions.

Mike

CC: Chris Rallis; David Barry

IND [redacted]

Fleischer 250
MAR 29 2000

Triangle Pharmaceuticals, Inc.
Attention: Anne F. McKay
4 University Place
4611 University Drive
Durham, NC 27707

Dear Ms. McKay:

Please refer to your Investigational New Drug Application (IND) submitted under 505(i) of the Federal Food, Drug, and Cosmetic Act for Coviracil® (emtricitabine) Capsules for the treatment of HIV.

In addition, please refer to IND serial submissions numbered 084, 085, 088, 089, 091, 092, and 093; teleconferences with the Division of Anti-Viral Drug Products (DAVDP) on December 27 and 28, 1999, and January 4 and 5, 2000; and to the January 12, 2000 meeting between representatives from Triangle Pharmaceuticals and DAVDP. All of these communications pertain to emerging safety data from the South African study FTC-302 ("A Randomized, Double Blind Equivalence Trial Comparing Emtricitabine to Lamivudine with a Triple Combination in Antiretroviral-Drug Naïve HIV-1 Infected Patients").

As you are aware, in the preceding communications we have expressed concerns regarding the safety of study subjects and have questioned the advisability of the continued conduct of study FTC-302. In particular, we queried your company regarding: whether the medical infrastructure at the sites in South Africa is adequate to support safe conduct of the clinical trial; details of the medical monitoring of study participants; and the potential role of emtricitabine (FTC), either alone or in combination with nevirapine, in the development of fatal and non-fatal hepatotoxicity. Questions about these issues ultimately highlighted the lack of involvement by a data safety monitoring board or other independent oversight committee and your failure to report some serious adverse events as required under CFR 312.32.

As discussed in our meeting on January 12, 2000, although the protocol for study FTC-302 was submitted under your IND [redacted] the study is being conducted exclusively at sites located in South Africa. Therefore, the principles for the ethical conduct of a clinical study in foreign countries discussed in CFR 312.120 ("Foreign clinical studies not conducted under an IND") are applicable to this circumstance, despite submission of the protocol to your U.S. IND. This has also made our assessment of the significance of some of the issues listed above, in the context of the setting and conditions of the study, very difficult. You will recall that at our meeting on January 12, we specifically asked you about your compliance with the requirements of the South African Medicines Control Council (MCC). To aid our understanding and assessment of the advisability of continuing study FTC-302 we contacted the MCC shortly after that meeting.

We are aware that the South African MCC contacted you following our initial communication with them. It is our understanding from your submission (SN 138), dated March 20, 2000, that the protocol for study FTC-302 has been recently amended to address safety concerns raised by the local authority. It is our understanding you are awaiting approval from the MCC to allow the protocol to proceed.

We are aware that you intend to submit the results from study FTC-302 in support of a future New Drug Application (NDA) for FTC as a treatment for HIV. While we are reassured by the MCC's current review of the safety of subjects in the study, we wish to remind you of our ongoing interest regarding the safe conduct of this study. Additional information will be required from study FTC-302 for the Division to allow its continuation under a U.S. IND and for it to be considered as a principal clinical trial in a future NDA. Specifically, you must:

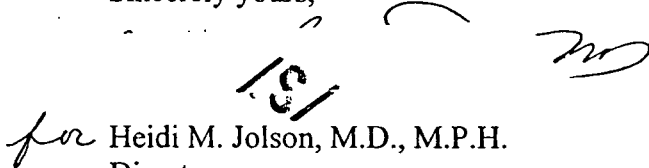
- Provide documentation from the South African regulatory authorities that the clinical trial has been conducted in accordance with their local laws and regulations and under conditions of good clinical practice.
- Demonstrate that the patients in South Africa are receiving appropriate medical care and follow-up.
- Document that investigators and patients are being adequately informed and updated on potential serious adverse events.
- Document all correspondence and interactions between Triangle [redacted] (the CRO), investigators and the South African regulatory authorities regarding the continuation of FTC-302 generally, and the actions taken to ensure safe patient management, specifically.
- Document that all serious adverse events occurring in studies involving FTC are being reported as outlined in CFR 312.32, regardless of attribution or possible causal association.
- Demonstrate that an independent review board has been formed to periodically review safety data from the study and make recommendations regarding human subject protection. All correspondence and/or records of this group's deliberations will need to be included in an NDA submission.
- Document that the hepatotoxicity seen in study FTC-302 has been fully and impartially investigated. We are aware that you are currently ascribing the development of hepatotoxicity to an approved antiretroviral, nevirapine. However, because the rate of serious hepatotoxicity significantly exceeds what is expected and reflected in the nevirapine label, you must investigate other explanations for the observed toxicity.


- Provide discussion of the applicability of safety results of FTC-302 to the U.S. population, particularly as part of an NDA submission.
- Fully discuss the impact of your protocol amendment to change concomitant antiretroviral use on the interpretation of efficacy results. A revised, detailed analysis plan should be submitted to the Division for review and comment, prior to conduct of any efficacy analyses.

Based on ongoing discussions between members of your staff and this division, we are generally aware that you have been working to address these requirements. However, in order to ensure full understanding on our part of your progress, we request that you provide a formal written response within thirty days of receipt of this letter in preparation for a face-to-face meeting.

Should you have any questions, please contact Ms. Leslie Stephens, R.N., M.S.N., Regulatory Management Officer, at (301) 827-2335.

Sincerely yours,

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

 Sandra L. Kweber, M.D.
Deputy Director
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Concurrence:

- HFD-104/Dir/Murphy
- HFD-530/DepDir/Birnkrant *DB 3/28/00*
- HFD-530/MTL/Cvetkovich *eso TC 3/28/00*
- HFD-530/MO/Fleischer *3/28/00*
- HFD-530/SCSO/DeCicco *MT For A.D 3/28/00*
- HFD-530/CSO/Stephens *MT For L.S. 3/27/00*

cc:

- IND [redacted]
- Division file
- HFD-530/Fleischer
- HFD-530/Stephens
- HFD-104/Kweder

Location: V:\DAVDP\CSO\Stephens\IND [redacted] Letters\000112regltr3.DOC

(AD) Advice

IND
CERTIFIED MAIL
RETURN RECEIPT REQUESTED

APR 12 2000

Triangle Pharmaceuticals, Inc.
Attention: Anne McKay
4 University Place
4611 University Drive
Durham, NC 27707

Dear Ms. McKay:

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Coviracil® (emtricitabine) Capsules for the treatment of HIV-1 infection.

In addition, please refer to the letters issued to your company dated November 4, 1999 and March 29, 2000 and to telephone facsimiles dated December 28, 1999; January 31, 2000 and February 7, 2000; and to the meeting between representatives of your company and the Division of Antiviral Drug Products (DAVDP) on January 12, 2000.

Please also refer to the telephone facsimile provided to us on April 6, 2000. This facsimile was a copy of a communication to you from the Executive Committee of the Medicines Control Council (MCC) of the Republic of South Africa recommending that study FTC-302, "A Randomized, Double Blind Equivalence Trial Comparing Emtricitabine to Lamivudine Within a Triple Combination in Antiretroviral Naïve HIV-1 Infected Patients," should be terminated.

Please make further reference to the teleconference between representatives of your company and DAVDP on April 6, 2000 during which you were informed that study FTC-302 is being placed on CLINICAL HOLD because of the recommendation of the MCC and because it presents an unreasonable and significant risk of illness or injury to the subjects enrolled in the trial [21CFR§312.42(b)(2)(i)(ii)]. Summarized below are the specific deficiencies and the information needed to resolve these deficiencies prior to removing this CLINICAL HOLD.

CLINICAL HOLD DEFICIENCIES

As you are aware, based on reports of three deaths and other reports of nonfatal hepatotoxicity in December 1999, DAVDP raised the following concerns about the conduct of study FTC-302:

1. The appropriateness of the medical management of subjects who experienced adverse events;
2. The adequacy of your investigation and reporting of adverse events;

3. The capacity of the medical infrastructure in South Africa to support the conduct of such a study;
4. The adequacy of communication between your company and the MCC; and,
5. The lack of a DSMB or other oversight board to review safety data and make recommendations regarding human subject protection.

At that time we also became aware that numerous serious adverse events (SAEs) had not been reported to us because of your interpretation of the reporting requirements under 21CFR§312.32. Subsequently, we met with you on January 12, 2000 in order to discuss resolution of the above concerns, and to reach agreement with you on study modifications that should be made to ensure the safe management of study subjects. Following this meeting, we additionally contacted the MCC to communicate our concerns regarding the conduct of trial FTC-302 and to request their perspective on this trial.

Although some modifications to the protocol were subsequently made and communication between the MCC and your company was established, our ongoing concerns regarding human subject protection in the clinical trial have remained, as we indicated in our letter of March 29, 2000. The recently reported deaths of subjects 3038 and 3069 raise renewed concern about the medical management of enrolled subjects and highlight a new concern about inappropriate trial enrollment.

We have also become aware that you have issued more than 350 protocol exemptions (waivers) to provide enrollment for subjects who did not otherwise meet protocol-specified eligibility criteria as written in FTC-302 (submission dated March 18, 1999, serial number 046). This excessive number and the type of protocol violations issued together raise questions about the integrity of the trial's conduct, and the future validity of its results. We are aware that the MCC has raised similar concerns on this issue.

Your facsimile of April 6, 2000 provides a preliminary recommendation from the Executive Committee of the MCC that trial FTC-302 be terminated. Importantly, even though this study was submitted to your U.S. IND, we acknowledge that the decisions regarding whether the study should continue, and how subjects currently enrolled in FTC-302 should be managed, remain under the jurisdiction of the MCC because the trial is being conducted exclusively at sites in South Africa.

We understand, however, your company will have the opportunity to present data to the MCC in the next few weeks that may ultimately alter this recommendation. Nonetheless, based on currently available information submitted to IND [redacted] we do not believe that trial FTC-302 is safe to proceed under your U.S. IND due to the concerns described above and in previous communications.

INFORMATION NEEDED TO RESOLVE CLINICAL HOLD

Until the MCC has completed their review and we have had the opportunity to inspect trial FTC-302 (which is scheduled for the week of April 10, 2000), we are unable to provide a complete list

of the information that will be required prior to lifting the CLINICAL HOLD. However, at a minimum, we anticipate requiring the following information:

1. Documentation of all findings and deliberations of the MCC's review of this trial.
2. Documentation of an MCC decision to allow the study to continue.
3. Satisfactory inspection of clinical trial sites audited by the MCC and the FDA, along with resolution of any unacceptable findings.
4. Establishment of an independent data safety monitoring board (DMSB).

Until you have submitted the required information, and we notify you that it is safe to proceed with this trial, you may not legally conduct study FTC-302 under your U.S. IND. We are aware that you are currently working with the MCC on appropriate medical management of patients currently enrolled in the trial. We will abide by the determination of the MCC in this regard, and request to be updated on these discussions as soon as possible.

Please identify your response to the clinical hold issue as a "CLINICAL HOLD COMPLETE RESPONSE." An incomplete response will not start the review clock. Your complete response submission should reference, by date, any information previously submitted necessary to fully respond to these clinical hold issues. To facilitate a response to your submission, submit this information in triplicate to IND [redacted]. In addition, send a copy of the cover letter to Ms. Leslie Stephens, Regulatory Project Manager.

Following receipt of your complete response to these issues, we will notify you of our decision within 30 days.


Please be further advised that regardless of whether the MCC decides that it is in the best interests of the study subjects to continue or to terminate study FTC-302, we believe that it is unlikely that study FTC-302 will provide pivotal data in support of a New Drug Application. We recommend that you request a teleconference or meeting with the Division to discuss the issues of applicability to the U.S. population that have been raised by this trial.

Correspondences to this IND can be sent to the following address:

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

Should you have any further questions concerning this IND, please contact Ms. Leslie Stephens, Regulatory Project Manager at (301) 827-2335. Please be advised that the division is available to discuss the further evaluation of this important safety issue with you, by teleconference or in a meeting, at your request.

Sincerely yours,


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

Concurrence:

- HFD-530/DepDir/Birnkrant *MB 4/12/00*
- HFD-530/MOTL/Cvetkovich *JC 4/12/00*
- HFD-530/MO/Fleischer *RF 4/12/00*
- HFD-530/CPMS/DeCicco *D 4-12-00*
- HFD-530/RPM/Stephens *MS 4/12/00*

cc:

- Archival IND [redacted]
- HFD-530/Division Files
- HFD-530/MOTL/Cvetkovich
- HFD-530/MO/Fleischer
- HFD-530/CPMS/DeCicco
- HFD-530/RPM/Stephens
- HFD-104/ADRA/Hassall

CLINICAL HOLD

Categories cited for Clinical Hold

(PUT AN "X" NEXT TO EACH CATEGORY THAT APPLIES)

- H1 X Medical Risk
- H2 ___ Pharm/tox
- H3 ___ Chemistry
- H4 ___ Microbiology
- H5 ___ Protocol Design
- H6 ___ Target Population
- H7 ___ Dose/Duration
- H8 ___ Route of Administration
- H9 ___ Other (specify briefly)
- HW ___ Waiver of Informed Consent

Location: V:\DAVDP\CSO\Stephens\IND [redacted] Letters\000412ho5.DOC

CLINICAL HOLD (HO)



Reed 7/17/00

GW 1240

REGISTRAR VAN MEDISYNE
DEPARTMENT VAN GESONDHEID
PRIVATE BAG X828
PRETORIA

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THE REGISTRAR OF MEDICINES
DEPARTMENT OF HEALTH
PRIVATE BAG X828
PRETORIA
0001
Dr. H Rees

Navrae • Inquiries: 14 April 2000.
Verwysing • Reference:

Triangle Pharmaceuticals
Ms Anne F McKay
4 University Place
Durham
NC 27707

MEDICINES CONTROL COUNCIL RESOLUTIONS - STUDY FTC-302

Dear Dr. McKay

Please find attached a letter of concern from the Medicines Control Council (MCC) with regards the above mentioned clinical trials study.

Yours faithfully

DR. HELEN REES
CHAIRPERSON; MCC

COUNCIL NOTES WITH CONCERN THAT IN STUDY FTC 302

There has been:

- Poor adherence to GCP
- Protocol violations regarding patient recruitment

RESOLVED:

1. That the study be terminated.
Therefore, there shall be no additional recruitment to the study.
2. Council further recommends that:
 - 2.1 The 27 patients who have been discontinued be followed up for safety till completion of 48 weeks from date of commencement. Patients who have been discontinued be not rechallenged with the same regimen.
 - 2.2 The study sites be re-examined by auditors of the MCC'S choice, at the expense of Triangle. Where the trialists have been found to perform suboptimally, consideration be given to transfer patients under their care to an alternative site.
 - 2.3 Patients showing a virological response (VL < 2000 copies/ml) on 2 consecutive visits to continue with their present regimen on compassionate grounds.
 - 2.4 Those continuing treatment be monitored as per most recent amendments to the protocol (Amendment 3) together with safety recommendations from Council resolutions of 4 March 2000.

All those who experience virological failure be followed up for safety for a period of 48 weeks from commencement of treatment.
 - 2.5 Council be notified of any further deaths immediately.
 - 2.6 A regular (monthly) safety report be submitted to Council.
 - 2.7 No retrospective amendment to the protocol be allowed.
 - 2.8 Triangle to cover costs of management of any serious adverse events.



DIE REGISTRATEUR VAN MEDISYNE
 DEPARTEMENT VAN GESONDHEID
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Navrae • Inquiries:
 Verwysing • Reference:

Dr. H Rees

07 August 2000

Triangle Pharmaceuticals
 Ms Anne F McKay
 4 University Place
 Durham
 NC 27707

MEDICINES CONTROL COUNCIL RESOLUTIONS – STUDY FTC-302

Dear Dr. McKay

Please find attached letters of resolutions from the Medicines Control Council (MCC) regarding the above-mentioned clinical trial study.

Yours faithfully

REGISTRAR OF MEDICINES

MEDICINES CONTROL COUNCIL RESOLUTION AT THE MEETING HELD
ON THE 21 JULY 2000.

COUNCIL RESOLVED:

1. That an independent audit must now be undertaken as a matter of urgency.
2. The compassionate use as recommended in the resolution implies an open label study - the study must be unblinded.
3. That this study was terminated and therefore the data will not be considered in any future registration application.
4. A letter be written re-affirming that the Council has stopped the trial.

APPEARS THIS WAY
ON ORIGINAL