

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-481

ADMINISTRATIVE DOCUMENTS
CORRESPONDENCE

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

NDA 21-481	Efficacy Supplement Type SE-	Supplement Number
Drug: Fuzeon™ (enfuvirtide) for Injection. Previously known as T-20.		Applicant: Hoffman-LaRoche, 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 type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority
• Chem class (NDAs only)		Type 1
• Other (e.g., orphan, OTC)		Type AA (HIV)
❖ User Fee Goal Dates		
		March 16, 2003
❖ Special programs (indicate all that apply)		
		<input type="checkbox"/> None <input type="checkbox"/> Subpart H <input checked="" type="checkbox"/> 21 CFR 314.510 (accelerated approval) <input type="checkbox"/> 21 CFR 314.520 (restricted distribution) <input checked="" type="checkbox"/> Fast Track <input checked="" type="checkbox"/> Rolling Review
User Fee Information		
• User Fee		<input checked="" type="checkbox"/> Paid
• User Fee waiver N/A		<input 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)	
• Exclusivity summary	Yes, sent to M. Holovac
• 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
Actions	
• Proposed action	(✓) AP () TA () AE () NA
• Previous actions (specify type and date for each action taken)	N/A
• Status of advertising (approvals only)	() Materials requested in AP letter (✓) Reviewed for Subpart H
Public communications	
• Press Office notified of action (approval only)	(✓) Yes () Not applicable
• 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 (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	N/A
• Most recent applicant-proposed labeling	✓
• Original applicant-proposed labeling	Not necessary
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews)	✓
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	N/A
Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	N/A
• Applicant proposed	✓
• Reviews	See Chemistry Review
Post-marketing commitments	
• Agency request for post-marketing commitments	✓
• Documentation of agreements relating to post-marketing commitments	✓
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	✓
❖ Memoranda and Telecons	✓
Minutes of Meetings	
• EOP2 meeting	✓
• Pre-NDA meeting CMC and Clinical meetings held separately, on same date	✓ June 11, 2002 (2)
• Pre-Approval Safety Conference	✓ January 15, 2003
• 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 Evaluation	
❖ 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 Evaluation	
❖ CMC review	✓
❖ Environmental Assessment	
• Categorical Exclusion	✓
• Review & FONSI	N/A
• Review & Environmental Impact Statement	N/A
❖ Micro (validation of sterilization & product sterility) review	✓
❖ Facilities inspection (provide EER report) See Chemistry Review	Date completed: (✓) Acceptable () Withhold recommendation
❖ Methods validation PENDING	() Completed (✓) Requested () Not yet requested
Other Reviews	
❖ Pharm/tox review, including referenced IND reviews	✓
❖ Nonclinical inspection review summary	✓
❖ Statistical review of carcinogenicity studies	✓
❖ CAC/ECAC report	✓

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Action Package Checklist

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

/s/

David Roeder
3/13/03 04:53:06 PM

**APPEARS THIS WAY
ON ORIGINAL**

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

DATE: 3-13-03

FROM: Debra Birnkrant, M.D.
Director, Division of Antiviral Drug Products, HFD-530

TO: Division File NDA 21-481

SUBJECT: Division Director's Memorandum for NDA for Fuzeon™ (enfuvirtide) for Injection for the Treatment of HIV in Treatment-Experienced Subjects

This memorandum is written in support of the accelerated approval of Fuzeon™ (enfuvirtide), for injection, a 36-amino acid synthetic peptide fusion inhibitor for the treatment of HIV-1 infection in treatment-experienced subjects with limited therapeutic options. This regulatory action is based on the favorable risk/benefit profile of the drug as determined by a multidisciplinary review of the totality of the data contained in NDA 21-481. This memorandum will focus on pivotal clinical trials T20-301 and T20-302 and an overall risk/benefit assessment will be described below.

BACKGROUND:

A NDA for Fuzeon™ was submitted in September, 2002. It received a 6-month priority review because it represents the first fusion inhibitor in its class and provides a treatment alternative for HIV infected subjects with resistance to currently available drug classes.

NDA 21-481 contained two principal studies, 301 and 302 which examined the use of Fuzeon™ in combination with individualized background therapy compared to individualized background therapy alone in treatment experienced subjects defined as having viremia following 3 to 6 months of prior therapy with all three classes of currently approved antiretrovirals or viremia and documented resistance or intolerance to at least one drug in each of the NRTI, NNRTI and PI classes of antiretrovirals. Both actively controlled studies were open label and subjects were randomized in a 2:1 randomization scheme of Fuzeon plus individualized background regimen versus individualized background alone. All subjects' individualized background regimens were based on history and genotypic and phenotypic testing at baseline; patients had received an average

of 12 antiretroviral medications prior to study entry. Both trials were designed as 48-week trials; 6-month data were reviewed for accelerated approval and the 48-week data will be submitted for traditional approval. There were only minor differences in enrollment criteria between the two trials. The trials were conducted in North and South America, Europe and Australia.

Of note, subjects in the individualized background arm who met criteria for virologic failure were allowed to switch to the Fuzeon™ arm. The primary endpoint for both studies was mean change in baseline HIV RNA.

TRIAL RESULTS: EFFICACY

In both principal trials, Fuzeon™ when added to individualized therapy was statistically significantly superior to individualized background alone. Pooled results will be presented because of the similarities in trial design.

The outcomes of randomized treatment at 24 weeks for HIV RNA were a decrease of 1.52 logs in HIV RNA for the Fuzeon™ containing arm compared to 0.73 logs in the individualized background arm. The percentage of patients achieving a \geq one log drop below baseline was 52% versus 26% for the Fuzeon™ and individualized background arms, respectively. Similar findings were seen in other endpoints including percent below 400 and 50 copies/ml (37% versus 16% and 23% versus 9%, respectively). Immunologically, Fuzeon™ plus individualized background showed significant results with a doubling in CD4 counts of +71 compared to +35 in subjects in the control arm.

TRIAL RESULTS: SAFETY

The safety database contains 1,153 adult subjects who received at least one dose of Fuzeon™ (as of March, 202); 608 subjects received the recommended dose for greater than 24 weeks. The database also includes information on 39 pediatric subjects. Similar to the efficacy data, safety data is based on a pooled analysis. Safety issues identified in the principal studies related to three key areas: injection site reactions (ISRs), an increase in pneumonia in arms containing Fuzeon™ and hypersensitivity reactions. ISRs occurred in 98% of subjects receiving Fuzeon™. Three percent of subjects discontinued treatment due to ISRs. The majority of subjects experienced their first ISR during the first week of treatment. ISRs were associated with mild to moderate pain, erythema, induration and nodules or cysts. Twenty-three percent of patients had six or more ISRs at any given time. Infection, including abscess and cellulitis was reported in 1% of subjects.

Hypersensitivity reactions occurred in less than 1% of subjects receiving Fuzeon™. Cases included rash, fever, nausea, vomiting, chills, hypotension, and elevated liver associated enzymes. Treatment emergent eosinophilia occurred in 11.2% of subjects receiving Fuzeon™ compared to 2.4% in the control group. Hypersensitivity reactions may occur upon rechallenge.

Overall, bacterial infections occurred at a low rate and equally between study arms. Correcting for exposure to Fuzeon™, given the study design of allowing patients to switch to Fuzeon™ after failing virologically, the risk of bacterial infections was 18 per 100 patient years in both treatment groups. However, there appeared to be an increase in the incidence of bacterial pneumonia in subjects who received Fuzeon™ compared to control. Bacterial pneumonia occurred at a rate of 4.68 per 100 person years compared to 0.61 per 100 patient years in the Fuzeon™ containing arm compared to control, respectively. This is consistent with rates of bacterial pneumonia in HIV seropositive patients found in the literature. Literature reports provided by the applicant indicate that the incidence of bacterial pneumonia in HIV seropositive patients is approximately 5 to 9 episodes per 100 person years. In HIV positive individuals with CD4 counts less than 200, the rate increases to 9 to 10 episodes per 100 patient years compared to 2 to 3 episodes per 100 patient years in the general population.

Both the applicant and the FDA reviewers examined potential causes for this discrepancy after the issue was identified by FDA. One hypothesis was that Fuzeon™ was an immunosuppressant. This hypothesis was considered to be unlikely based on similar rates of overall bacterial infections in both the Fuzeon and control arms. Further, the incidences of neutropenia and lymphopenia were not increased in the Fuzeon™ arm. Lastly, the diverse infections seen were not consistent with any known immunodeficiency states and nonclinical data did not identify any conditions associated with immunodeficiencies. A more likely hypothesis relates to potential bias in trial design. Both 301 and 302 allowed for subjects in the control group to switch to the Fuzeon™ containing arm if they failed virologically. This would mean that only healthier subjects would remain on the individualized background arm. When the comparison was made between the Fuzeon™ containing arm and the individualized background control, two distinctively different populations were being compared, that is, a population who could be failing virologically on the Fuzeon™ containing arm and a population who was not failing on the individualized background arm. Thus, bias may have been introduced into the data analysis.

Two other areas deserve comment, resistance and mortality. With regard to mortality, there were 10 deaths in the Fuzeon™ containing arm and 5 deaths in the control arm during the first 24 weeks of therapy. Two of the ten deaths were due to bacterial pneumonia in the Fuzeon™ containing arm. Of these, one patient developed an aspiration pneumonia following a seizure and the other patient had chronic lung infections due to Pseudomonas in a setting of bronchiectasis. Other causes of death are described in the medical officer's review and are mostly consistent with advanced HIV disease.

Development of resistance to Fuzeon™ was seen in clinical trials submitted in this NDA. Post-treatment plasma samples were examined for viral genotype from those subjects meeting the protocol definition of virologic failure. Matched

sequence data were obtained from 218 subjects in the phase 3 clinical trials. The majority of these subjects had virus post-treatment with an altered genotype in the codons for gp41 amino acids 36-45. The successful clinical trial results indicate that HIV-1 pays a high price in fitness to replicate in the presence of Fuzeon™. Resistance to Fuzeon™ may be more likely to develop in those subjects who use it as functional monotherapy instead of combining it with other active medications. Cross resistance to other approved classes of antiretrovirals has not been seen; cross resistance to another fusion inhibitor, T-1249, has also not been seen to date.

RISK/BENEFIT ASSESMENT:

To date, there are limited treatment options for patients with advanced HIV disease. There is clearly a need for new antiretroviral therapies with different mechanisms of action to overcome current resistance issues faced by HIV infected subjects. Fuzeon™ provides statistically and clinically significant reductions in viral load as determined by a review of 24-week data contained in the NDA. With regard to safety, given the patient population for which this new drug is indicated and the lack of definitive immunosuppressant properties in the setting of a potentially biased study design, the risk benefit profile allows me to support approval of this marketing application. Although there may be a safety signal with regard to pneumonia, this can be studied post-approval with appropriate warnings placed in product labeling because the benefits of the antiviral effect likely outweigh the infrequent risk of pneumonia.

In sum, Fuzeon™ represents a new class of antiretroviral agent for treatment of HIV infected patients with limited treatment options. Benefit was clearly demonstrated in controlled clinical trials in patients with ongoing viral replication despite antiretroviral therapy. The safety profile is acceptable in the population in whom it is indicated. The applicant has prepared extensive educational materials that adequately explain the risk/benefit profile of this new therapy. Post-marketing commitments are described below.

**APPEARS THIS WAY
ON ORIGINAL**

PHASE 4 COMMITMENTS:

Clinical and Pharmacology/Toxicology

1. Please submit the complete protocol for the clinical cohort study you have described in outline form, "*Observational Cohort Study on the Incidence of Pneumonia in HIV-1 Infected Patients Treated with Fuzeon.*" Following FDA review, this study will be initiated shortly after the product launch of enfuvirtide and completed in a time frame specified in the protocol.

Protocol Submission: Within 4 months of the date of this letter

Final Report Submission: Within 48 months of the date of this letter

2. Please conduct a general-purpose immune suppression screening assay such as a T-cell dependent antibody-forming assay, and provide the results within 12 months of the date of this letter. If results of this study show evidence of impairment of immune response, a more specific host resistance assay using an appropriate animal model for upper-respiratory bacterial infections must be conducted.

Protocol Submission: Within 3 months of the date of this letter

Final Report Submission: Within 12 months of the date of this letter

3. Please submit the results of study T20-305, "*Intervention substudy: A Phase 3, Open-label Safety Study of T-20/Ro 29-9800 (HIV-1 fusion inhibitor) in combination with Oral Antiretrovirals, in Patients Who are Unable to Construct a Viable Regimen*", with appropriate suggested changes to the product insert and all patient educational materials based on the results of this study. Additional follow-up studies may be needed to formally assess interventions that may reduce the occurrence or severity of local injection site reactions.

Final Report Submission: Within 9 months of the date of this letter

Pharmacokinetics

4. Provide additional pharmacokinetic data in children less than six years old.

Protocol Submission: Within 4 months of the date of this letter

Final Report Submission: Within 28 months of the date of this letter

The following request will be added to the action letter, but not listed under the postmarketing commitments:

- Please include an integrated assessment of adverse reactions with each post approval quarterly mandated report. The assessment should include all reports of adverse events from ongoing clinical trials, postmarketing spontaneous reports, and literature reports. Particular attention should be paid to infectious complications, hypersensitivity reactions, and atypical injection site reactions. The assessment should also include any suggested changes to the product insert and all patient educational materials based on the integrated review. This requirement will be reassessed 36 months from the date of this letter.

**APPEARS THIS WAY
ON ORIGINAL**

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

/s/

Debra Birnkrant
4/10/03 09:39:25 AM
MEDICAL OFFICER

sign off please

Mark Goldberger
4/15/03 10:23:08 AM
MEDICAL OFFICER

**APPEARS THIS WAY
ON ORIGINAL**

NDA 21-481

Medical Team Leader's New Drug Application Memorandum

Trade Name: Fuzeon
Established Name: Enfuvirtide
Applicant: Hoffmann-LaRoche, Inc.

Date Submitted: September 16, 2002
Date Completed: March 7, 2003

I fully concur with the conclusion of Dr. Melisse Baylor's Medical Officer Review of NDA 21-481 that enfuvirtide should be approved for the treatment of HIV-infected patients in treatment experienced adults with ongoing viral replication. Although there are significant safety concerns regarding enfuvirtide, the potential benefit from enfuvirtide use outweighs the known safety concerns. However, in order to optimize the relative safety and efficacy of enfuvirtide, a strong risk-management program must be in place with approval to ensure that potential safety hazards associated with enfuvirtide use are minimized.

The antiretroviral activity of enfuvirtide has been well-documented in two large Phase 3 studies. Subjects enrolled in both studies had advanced HIV disease with substantial prior exposure to antiretroviral therapy. The magnitude of the antiviral effect observed (an approximately 0.85 log attributable to enfuvirtide), coupled with immunological improvement, makes it very likely that the drug will have clinical efficacy. A similar effect size was seen subjects with higher or lower viral load at entry, i.e., above or below 40,000 copies/mL.

The major concerns regarding enfuvirtide use are safety issues: these include localized injection site reactions, hypersensitivity reactions, and pneumonia. As well described by Dr. Baylor, local injection site reactions (ISRs) to enfuvirtide are nearly universal. It is surprising that relatively so few subjects discontinued therapy in the phase 3 trials given the frequency and severity of these reactions (added to the difficulty of twice daily self-injections). The low rate of study discontinuation due to ISRs may have been related to the subjects' commitment to the clinical trial and the limited alternative treatment options available to participants.

The applicant has done an admirable job of addressing the risk management of ISRs in clinical practice through extensive patient and practitioner educational materials. We have reviewed these materials and believe they represent an excellent attempt to educate both patients and health care professionals regarding enfuvirtide. Nevertheless, complications of injection site reactions will need to be closely monitored post approval to ensure that a different picture than what has emerged from phase 3 studies is not encountered with more heterogeneous patient populations in less structured clinical environments. As wider experience with enfuvirtide accrues, different approaches to risk management may be necessary, e.g., additional, more targeted patient education materials may be necessary.

The second safety concern identified in the phase 3 clinical studies is the risk of allergic/hypersensitivity reactions from enfuvirtide use. Dr. Baylor and the applicant have both analyzed these reports thoroughly, and all patient and professional educational materials make this potential risk clear. In absolute terms the risk is low and does not outweigh the benefit from enfuvirtide; however, similar to abacavir (where hypersensitivity reactions are estimated to be far more common), practitioners and patients must be aware of this potential adverse effect so that possible reactions can be rapidly recognized and addressed. Although no deaths due to hypersensitivity/allergic reactions were seen in Phase 3 studies, reactions have occurred on rechallenge and vigilance to identify allergic reactions must remain high.

The last safety concern, and perhaps the most difficult to assess at this time, is the potential immunosuppressive effect of enfuvirtide. As Dr. Baylor summarizes, there was clearly a greater relative risk of pneumonia in subjects receiving enfuvirtide plus optimized background (OB) compared to subjects receiving optimized background alone. In contrast, overall bacterial infections were similar in both treatment arms. There are several reasons to suspect that the finding of a relatively increased risk of pneumonia is specious. Most apparent is the experimental design used in both Phase 3 studies; since subjects in the optimized background arm could cross over to the enfuvirtide arm, over time potentially 'healthier/enriched' subjects remained in the OB arm relative to the enfuvirtide arm. A second reason that this result may be incorrect is the absolute low incidence of pneumonia in the OB arm; rather than an increased rate of pneumonia in the enfuvirtide arm (suggestive of immunosuppression), the low incidence of pneumonia in the OB arm implies that there may have been a spuriously low occurrence of pneumonia in the OB arm. Comparison of the enfuvirtide vs. control arms would then yield the (incorrect) conclusion that enfuvirtide + OB was associated with an immunosuppressive effect. The last factor arguing against an immunosuppressive effect is the absence of a biological rationale at this time; consistent with this is the lack of any finding from previous animal studies consistent with an immunosuppressive effect.

Despite this, the possibility of an immunosuppressive effect cannot be excluded. This is especially true since a greater risk of pneumonia was observed independently in both Phase 3 studies. In addition, as the first member of a new antiretroviral class to be approved, there is no experience with similar drugs to serve as precedent. The applicant proposes to address this concern in several ways. Post-marketing commitments to study the relationship of pneumonia to enfuvirtide use in both a large clinical cohort study and in animal studies have been outlined. The applicant has also proposed prominent mention of pneumonia risk in the package insert and professional materials. This approach appears appropriate for risk management post-approval. The absolute incidence of pneumonia that was seen in the Phase 3 studies must also be considered: even if a relative increase in the risk of pneumonia is confirmed, the risk is at best modest and would not outweigh the potential benefit from enfuvirtide use in individual patients.

Another concern less readily labeled as a safety issue but nonetheless significant is the development of resistance to enfuvirtide, as discussed in both Dr. Battula's microbiology review and in Dr. Baylor's clinical review. Resistance to enfuvirtide was well documented in the Phase 3 trials, and is likely a function of the number of active components in the background regimen. (Analysis of virological response by degree of resistance at baseline, as described in Dr. Hammerstrom's statistical review, clearly shows a better response as more genotypically sensitive or phenotypically sensitive agents are

available in the background regimen.) Following the development of resistance to enfuvirtide, it is possible that patient isolates will also be cross-resistant to future entry inhibitors, a significant possible adverse consequence of enfuvirtide use. However, this predominantly theoretical risk should not contraindicate approval but should be clearly noted in the package insert. It is significant in this regard that preliminary data for another entry inhibitor, T-1249, shows *in vivo* activity in patients previously exposed to enfuvirtide (as reported recently at the 10th Conference on Retroviruses and Opportunistic Infections).

Overall Recommendation:

My overall recommendation, in concurrence with Dr. Baylor, is that enfuvirtide be approved for the indication of treatment of HIV-1 infection in treatment experienced patients with viremia despite ongoing therapy. Although I have significant concerns regarding certain safety issues and the emergence of resistance, there is little question the agent is an effective antiretroviral. It is likely that primary clinical use will be in patients with relatively advanced disease who have limited options but for whom other active agents can be identified to establish an effective combination regimen, although substantial rises in CD4 cells were seen even in very advanced subjects. Enfuvirtide may also be a valuable component of combination regimens with newer treatments as they become available.

Steven R Gitterman, M.D., Ph.D.
Medical Team Leader

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ON ORIGINAL**

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

/s/

Steven Gitterman
3/12/03 03:45:38 PM
MEDICAL OFFICER

Any questions, PLEASE don't hesitate to call

Debra Birnkrant
3/13/03 10:40:11 AM
MEDICAL OFFICER

ON ORIGINAL

EXHIBIT A1**PATENT INFORMATION FOR NDA NO. 21-481**

1)	Active Ingredient(s)	enfuvirtide
2)	Strength(s)	90 mg
3)	Trade Name	FUZEON™
4)	Dosage Form and Route of Administration	Lyophilized powder for injection
5)	Applicant (Firm) Name	Hoffmann-La Roche Inc.
6)	NDA Number	NDA 21-481
7)	First Approval Date	Not yet approved*
8)	Exclusivity: Date first ANDA could be submitted	ANDA can not be submitted for at least five (5) years from the date pending NDA is approved
9)	Patent Information	See Attachment

CONFIDENTIAL INFORMATION

*Since the New Drug Application has not yet been approved, this submission is considered as constituting trade secrets or commercial or financial information which is privileged or confidential within the meaning of the Freedom of Information Act (5 USC 552). It is requested that this submission not be published until the New Drug Application has been approved.

Rev. 12/97

[Use with New Chemical Entities]

53246

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ATTACHMENT 1 TO EXHIBITS A1-A3**First US Patent Number: 5,464,933****Expiration Date: June 7, 2013****Type of Patent-Indicate all that apply (check applicable boxes):**

- | | | | | | |
|----|--|-------------------------------------|---|--------------------------|---|
| 1. | Drug Substance (Active Ingredient) | <input checked="" type="checkbox"/> | Y | <input type="checkbox"/> | N |
| 2. | Drug Product (Composition/Formulation) | <input type="checkbox"/> | Y | <input type="checkbox"/> | N |
| 3. | Method of Use | <input type="checkbox"/> | Y | <input type="checkbox"/> | N |

Name of Patent Owner: Trimeris, Inc.**Second US Patent Number: 6,133,418****Expiration Date: June 7, 2013****Type of Patent-Indicate all that apply:**

- | | | | | | |
|----|--|-------------------------------------|---|--------------------------|---|
| 1. | Drug Substance (Active Ingredient) | <input checked="" type="checkbox"/> | Y | <input type="checkbox"/> | N |
| 2. | Drug Product (Composition/Formulation) | <input checked="" type="checkbox"/> | Y | <input type="checkbox"/> | N |
| 3. | Method of Use | <input type="checkbox"/> | Y | <input type="checkbox"/> | N |

Name of Patent Owner: Trimeris, Inc.**The following declaration statement is required if the above listed patent has Composition/Formulation or Method of Use claims.**

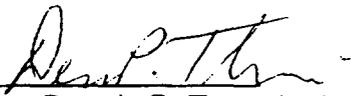
The undersigned declares that the above stated United States Patent Number 6,133,418 covers the composition, formulation and/or method of use of enfuvirtide. This product is:

- currently approved under the Federal Food, Drug, and Cosmetic Act.)

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OR

the subject of this application for which approval is being sought.)

By: 

Name: Dennis P. Tramaloni

Date: August 7, 2002

Title: Senior Counsel & Managing Attorney

Telephone Number: (973) 235-4475

**APPEARS THIS WAY
ON ORIGINAL**

April 11, 2003

Addendum added
to action package



Dr. Debra Birnkrant, Division Director
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, MD 20850

PATENT INFO.

Dear Dr. Birnkrant:

Re: **NDA 21-481 - FUZEON™ (enfuvirtide, Ro 29-9800) for Injection**
OTHER: Updated Patent Information

Reference is made to Hoffmann-La Roche Inc.'s New Drug Application (NDA) 21-481 for FUZEON™ (enfuvirtide, Ro 29-9800) for Injection. Reference is also made to the Agency's approval letter dated March 13, 2003.

The patent information, which was previously submitted within the Rolling NDA submission on September 13, 2002, has been revised to include the following significant changes.

1. The attached updated patent information is being filed within 30 days of the approval of NDA 21-481.
2. The appended patent information has been updated to include a third U.S. Patent (No. 6,475,491) which issued after the completed filing of Applicants NDA.
3. The updated patent information has also been amended to correct the identity of the owner of the first two listed patents. Duke University is the record owner of these two patents and Trimeris Inc. is the exclusive licensee thereunder. Trimeris Inc. owns the third listed patent.

Should you have any questions concerning this submission, please feel free to contact the undersigned.

Sincerely,

HOFFMANN-LA ROCHE INC.

Robin L. Conrad
Group Director,
Drug Regulatory Affairs
(973) 562-3676
(973) 562-3700 (fax)

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RLC/EMD
Attachments
HLR No. 2003-1152
Desk Copy: Virginia Yoerg

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EXHIBIT A1

UPDATED PATENT INFORMATION FOR NDA NO. 21-481

1)	Active Ingredient(s)	enfuvirtide
2)	Strength(s)	90 mg
3)	Trade Name	FUZEON
4)	Dosage Form and Route of Administration	white to off-white sterile lyophilized powder for reconstitution with 1.1 mL Sterile Water for Injection for subcutaneous administration
5)	Applicant (Firm) Name	Hoffmann-La Roche Inc.
6)	NDA Number	21-481
7)	First Approval Date	March 13, 2003
8)	Exclusivity: Date first ANDA could be submitted	ANDA can not be submitted for at least five (5) years from the date pending NDA is approved
9)	Patent Information	See Attachment

**APPEARS THIS WAY
ON ORIGINAL**

ATTACHMENT 1 TO EXHIBIT A1

First US Patent Number: 5,464,933

Expiration Date: June 7, 2013

Type of Patent-Indicate all that apply (check applicable boxes):

- | | | | | | |
|----|--|-------------------------------------|---|--------------------------|---|
| 1. | Drug Substance (Active Ingredient) | <input checked="" type="checkbox"/> | Y | <input type="checkbox"/> | N |
| 2. | Drug Product (Composition/Formulation) | <input type="checkbox"/> | Y | <input type="checkbox"/> | N |
| 3. | Method of Use | <input type="checkbox"/> | Y | <input type="checkbox"/> | N |

Name of Patent Owner: Duke University

Second US Patent Number: 6,133,418

Expiration Date: June 7, 2013

Type of Patent-Indicate all that apply:

- | | | | | | |
|----|--|-------------------------------------|---|--------------------------|---|
| 1. | Drug Substance (Active Ingredient) | <input checked="" type="checkbox"/> | Y | <input type="checkbox"/> | N |
| 2. | Drug Product (Composition/Formulation) | <input checked="" type="checkbox"/> | Y | <input type="checkbox"/> | N |
| 3. | Method of Use | <input type="checkbox"/> | Y | <input type="checkbox"/> | N |

Name of Patent Owner: Duke University

The following declaration statement is required if the above listed patent has Composition/Formulation or Method of Use claims.

The undersigned declares that the above stated United States Patent Number 6,133,418 covers the composition, formulation and/or method of use of enfuvirtide. This product is:

currently approved under the Federal Food, Drug, and Cosmetic Act.

OR

the subject of this application for which approval is being sought.

By: 
Name: Dennis P. Tramaloni
Date: August 7, 2002
Title: Senior Counsel & Managing Attorney
Telephone Number: (973) 235-4475

Third US Patent Number: 6,475,491

Expiration Date: June 7, 2015

Type of Patent-Indicate all that apply:

- | | | | | | |
|----|--|-------------------------------------|---|--------------------------|---|
| 1. | Drug Substance (Active Ingredient) | <input type="checkbox"/> | Y | <input type="checkbox"/> | N |
| 2. | Drug Product (Composition/Formulation) | <input type="checkbox"/> | Y | <input type="checkbox"/> | N |
| 3. | Method of Use | <input checked="" type="checkbox"/> | Y | <input type="checkbox"/> | N |

If patent claims method(s) of use, please specify approved uses or uses for which approval is being sought that are covered by patent: treatment of HIV infection.

Name of Patent Owner: Trimeris, Inc.

The following declaration statement is required if the above listed patent has Composition/Formulation or Method of Use claims.

The undersigned declares that the above stated United States Patent Number 6,475,491 covers the composition, formulation and/or method of use of enfuvirtide. This product is:

currently approved under the Federal Food, Drug, and Cosmetic Act.

OR

the subject of this application for which approval is being sought.

By: 
Name: Dennis P. Tramaloni
Date: August 7, 2002
Title: Senior Counsel & Managing Attorney
Telephone Number: (973) 235-4475

DEBARMENT CERTIFICATION

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

**APPEARS THIS WAY
ON ORIGINAL**

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

Form Approved OMB No. 0910-0297
Expiration Date: February 29, 2004

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>

<p>1 APPLICANT'S NAME AND ADDRESS</p> <p>Dr. Katrin Rupalla Senior Program Manager Drug Regulatory Affairs Hoffmann-La Roche Inc. 340 Kingsland Street Nutley, New Jersey 07110-1199</p>	<p>4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER</p> <p>NDA 21-481</p>	
<p>2 TELEPHONE NUMBER (Include Area Code)</p> <p>(973) 562-2139</p>	<p>5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p>IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.</p> <p>IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW</p> <p><input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.</p> <p><input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:</p> <p>_____</p> <p>(APPLICATION NO. CONTAINING THE DATA.)</p>	
<p>3 PRODUCT NAME</p> <p>TRADENAME (enfuvirtide)</p>	<p>6. USER FEE I.D NUMBER</p> <p>24904749</p>	
<p>7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.</p> <p><input type="checkbox"/> A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)</p> <p><input type="checkbox"/> A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE (See item 7, reverse side before checking box.)</p> <p><input type="checkbox"/> 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.)</p> <p><input type="checkbox"/> 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.)</p> <p><input type="checkbox"/> THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY (Self Explanatory)</p>		
<p>8 HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p> <p>(See Item 8, reverse side if answered YES)</p>		
<p>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:</p> <p>Department of Health and Human Services Food and Drug Administration CBER, HFM-99 1401 Rockville Pike Rockville, MD 20852-1448</p> <p>Food and Drug Administration CDER, HFD-94 and 12420 Parklawn Drive, Room 3046 Rockville, MD 20852</p> <p>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.</p>		
<p>SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE</p> <p><i>K Rupalla</i></p>	<p>TITLE</p> <p>Senior Program Manager</p>	<p>DATE</p> <p>June 24, 2002</p>

BEST POSSIBLE COPY

PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

NDA/BLA # : 21-481 Supplement Type (e.g. SE5): _____ Supplement Number: _____

Stamp Date: September 16, 2002 Action Date: March 13, 2003

HFD-530 Trade and generic names/dosage form: Fuzeon (enfuvirtide) for Injection, 90 mg

Applicant: Hoffman-LaRoche, 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 children 6 years of age and older

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. five 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: _____

Date studies are due (mm/dd/yy): 12/31/04, as stated in the January 19, 2001 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
3/13/03 04:29:25 PM

**APPEARS THIS WAY
ON ORIGINAL**

EXCLUSIVITY SUMMARY for NDA # 21-481 SUPPL #

Trade Name Fuzeon™ Generic Name enfuvirtide

Applicant Name Hoffman-LaRoche, Inc. HFD-530

Approval Date March 13, 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).

APPEARS THIS WAY
ON ORIGINAL

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: _____

Signature of Preparer
Title: Regulatory Health Project Manager

3/5/03
Date

[/S/]

Signature of Office or Division Director

3/13/03
Date

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

**APPEARS THIS WAY
ON ORIGINAL**

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

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

/s/

Debra Birnkrant
3/21/03 08:42:07 AM

APPEARS THIS WAY
ON ORIGINAL

DSI CONSULT: Request for Clinical Inspections

Date: August 2, 2002

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

Through: Joanne Rhoades, M.D., Ph.D., Director, DSI/HFD-45

From: Virginia L. Yoerg, Review Division PM
Division of Antiviral Drug Products, HFD-530

Subject: **Request for Clinical Inspections**
NDA 21-481
Sponsor: Hoffman-La Roche, Inc.
Drug: Fuzeon (T-20, enfuvirtide, previously Ro 29-9800)

Protocol/Site Identification:

As discussed with you, the following protocols/sites essential for approval have been identified for inspection. These sites are listed in order of priority. Please select four out of the six identified domestic sites, preferably the first four listed.

Indication	Protocol #	Site (Name and Address)
Treatment of HIV-1 infection	T20-301/NV16054	[]
Treatment of HIV-1 infection	T20-301/NV16054	[]
Treatment of HIV-1 infection	T20-301/NV16054	[]
Treatment of HIV-1 infection	T20-301/NV16054	[]

Treatment of HIV-1 infection	T20-301/NV16054	[]
Treatment of HIV-1 infection	T20-301/NV16054	[]

Note: International inspection requests or requests for five or more inspections require sign-off by the ORM Division Director and forwarding through the Director, DSI.

International Inspections: Not applicable

Goal Date for Completion:

We request that the inspections be performed and the Inspection Summary Results be provided by (inspection summary goal date) **December 05, 2002**. We intend to issue an action letter on this application by (action goal date) **December 20, 2002**. Please note that this NDA is under rolling review, and the clock is expected to start on August 30, 2002.

Should you require any additional information, please contact Virginia L. Yoerg at (301) 827-2419 or write to yoergv@cder.fda.gov (email).

Concurrence: (if necessary)

Steven Gitterman, M.D., Medical Team Leader
Melisse Baylor, M.D., Medical Reviewer
Virginia L. Yoerg, Regulatory Health Project Manager

**APPEARS THIS WAY
ON ORIGINAL**

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

/s/

Steven Gitterman
8/9/02 06:18:36 PM

APPEARS THIS WAY
ON ORIGINAL



Record of Industry Meeting

Date of Meeting: March 10, 2000

IND: _____

Drug: T-20

Indication: Treatment of HIV-1 infection

Sponsors: Trimeris Inc. and Roche

Type of Meeting: Clinical Development Meeting (Phase 2)

FDA Attendees and Titles:

Heidi Jolson, M.D., M.P.H., Division Director, Division of Antiviral Drug Products (DAVDP)
Debra Birnkrant, M.D., Acting Deputy Director, Clinical, DAVDP
Therese Cvetkovich, M.D., Medical Team Leader, DAVDP
Joseph Toerner, M.D., Medical Officer, DAVDP
Narayana Battula, Ph.D., Microbiologist, DAVDP
Lauren Iacono-Connors, Ph.D., Microbiology Team Leader, DAVDP
Z. Jonathan Ma, Ph.D., Mathematical Statistician, Division of Biometrics
Greg Soon, Ph.D., Mathematical Statistician, Division of Biometrics
Robert O. Kumi, Ph.D., Pharmacokinetics Reviewer, DAVDP
Teresa Wu, M.D., Medical Officer, DAVDP
David Morse, Ph.D., Pharmacologist, DAVDP
Melissa Truffa, R.Ph., Regulatory Project Manager, DAVDP
Charles Frost, Pharm.D., Visiting Post-Doctoral Fellow

External Constituent and Titles:

Dani Bolognesi, Ph.D., Chief Executive Officer and Chief Scientific Officer, Trimeris
Joan Drucker, M.D., Chief Medical Officer and Director of Clinical Trials, Trimeris
Janice Geary, Clinical Research Manager, Trimeris
Sam Hopkins, Ph.D., Vice President, Medical Affairs, Trimeris
Carol Ohmstede, Ph.D., Manager, Strategic Planning, Trimeris

Jain Chung, Ph.D., Biostatistician, Roche
Robin Conrad, Program Director, Regulatory Affairs, Roche
John Hakimi, Ph.D., Life Cycle Leader, Roche
Miklos Salgo, M.D., Clinical Science Leader, Roche

Background

On January 28, 2000, Trimeris requested a meeting with the Division of Antiviral Drug Products (DAVDP) to discuss key design elements of draft Phase 3 protocols for T-20. A pre-meeting package was submitted January 28, 2000 (SN 050) that included issues for discussion. These issues as outlined below were discussed following a brief presentation by the sponsor.

For each discussion topic, the sponsor's question is shown in regular font, followed by DAVDP's response in bold font.

Discussion

1. Choice of Comparator: The sponsor proposes that an "Optimized Background" (OB) regimen chosen by the physician and patient, based on the patient's baseline viral genotypic/phenotypic antiviral resistance testing and prior treatment history is an appropriate comparator arm for studies T20-301/NV16054 and T20-302/NV16052.

The Division agrees that the proposed "Optimized Background" (OB) regimen chosen, by the physician and patient, based on the patient's baseline viral genotypic/phenotypic antiviral resistance testing, and based on prior treatment history, is an appropriate comparator arm. In addition, we recommended that they minimize the variability in the phenotypic sensitivity score (PSS). One suggestion would be to have samples evaluated at a central laboratory site for evaluation.

The sponsor plans to use a central laboratory that provides the commercially available phenotypic sensitivity testing.

DAVDP agrees with the sponsor's plans to study treatment-experienced patients. We discussed limiting the patient population to patients who have experience with all three classes of antiretroviral agents. Further discussions of enrolling patients who are naïve to one antiretroviral class will occur as the development of T-20 proceeds.

2. Choice of Comparator: The sponsor also proposes that it is appropriate to allow a pre-specified list of experimental agents to be included as part of the optimized background regimen.

DAVDP agrees that this approach would represent the standard of care in this experienced patient population. However, we would expect the treatment groups to be well-balanced with regard to the use of experimental agents and that the number of study participants should be large enough to provide for this balance among treatment groups. The sponsor has considered the use of a fixed background regimen as an alternative study design. Further detailed statistical discussions will occur as plans for their phase 3 studies become better defined.

3. Rationale for Unblinded, Non-Placebo Controlled Studies: The sponsor proposes that it is not appropriate to conduct the pivotal registration studies, T20-301/NV16054 and T20-302/NV16052 as blinded, placebo-controlled trials.

The Division acknowledges the obstacle to conducting blinded studies involving T-20 because it is administered as large-volume subcutaneous injections. The difficulties in conducting open-label studies were outlined. Methods to encourage study subjects randomized to the optimized background alone to maintain therapy were discussed. Of greatest concern is the likely disproportionate drop-out rate from the control arm in order that study subjects receive T-20 as part of their therapy. There appears to be little incentive for subjects to remain on the control arm.

4. Study endpoints relevant to the population being tested: The sponsor proposes that in a heavily pre-treated patient population such as that included in protocols T20-301/NV16054 and T20-302/NV16052 the following primary efficacy endpoint appropriate:

Absolute improvement of the T-20 + OB regimen alone, measured by the percentage of patients with either a 1 log₁₀ drop in plasma HIV-1 RNA from baseline or plasma HIV-1 RNA < 400 copies/mL at or before week 24 with no virologic rebound by week 24.

Appropriate primary endpoints for treatment experienced patients is an evolving issue within DAVDP. The proposal to use a 1 log reduction in plasma RNA as the primary endpoint for pivotal studies may be appropriate for this patient population. However, the reduction must be sustained. In addition, in order to establish a firm baseline plasma HIV RNA to determine the primary endpoint, the baseline plasma HIV RNA determination should be based on more than one measurement.

The sponsor indicated that the primary endpoint for their pivotal studies would be determined by the DSMB after an interim review of the 12-week data from the Phase 3 studies. The Division strongly discourages a change in the primary endpoint based upon an interim analysis.

The sponsor indicated that they would submit revised protocols to the Division addressing above-mentioned issue for review and comment.

5. Meaningful Clinical Benefit: The sponsor proposes that demonstration of a 15% absolute improvement of the T-20 containing arm over the comparator arm constitutes a clinically meaningful benefit to support approval of T-20/Ro 29-9800.

DAVDP agreed that a 15% absolute improvement of the T-20 arm over the comparator arm could represent a clinically meaningful benefit provided that the primary endpoint used is the proportion of subjects with 1 log below baseline HIV RNA or the proportion of patients below the level of HIV RNA detection.

An anticipated smaller treatment effect may require a larger absolute improvement in order to constitute a clinical meaningful benefit.

Other Discussions

1. The Division noted that study participants would be responsible for paying for the antiretroviral agents that comprise their OB therapy. We encouraged the sponsor to consider paying for study drugs in some fashion in order to assist patients in maintaining their OB regimen and minimize discontinuation because of the expense of study drug combinations. The sponsor agreed to consider this and other incentives to maintain patients enrolled in the study.
2. Enrollment into the ACTG sponsored pediatric study using T-20 has been slow. The sponsor indicated that the ACTG was currently reviewing a protocol amendment in order to facilitate enrollment. DAVDP offered to review and comment on the draft protocol amendment if this would be useful to the sponsor.
3. The Division is interested in reviewing any data the sponsor has compiled on injection site adverse reactions. The sponsor indicated that they would submit the available data as requested. In addition, we inquired about whether there were data on therapy for local reactions caused by the injection of T-20. The sponsor indicated that these reactions were treated in different ways depending on the investigator and that there were no standardized recommendations for treatment at this time.
4. The sponsor was planning for an End of Phase 2 meeting in June 2000 when additional data were available. A revised draft Phase 3 protocol incorporating revisions based on today's discussion will be submitted prior to the End of Phase 2 meeting.
5. Indications: Comments on the labeling for T-20 are premature at this time and will be based on the review of efficacy and safety data from clinical trials.

Minutes preparer: _____ Date: _____

**APPEARS THIS WAY
ON ORIGINAL**

Enclosures:
List of Attendees
Sponsor's slide presentation

Concurrence:

HFD-530/MO/Toerner edited 6/6/00 eso 6/6/00 jt
HFD-530/MOTL/Cvetkovich 6/14/00 tc
HFD-530/DivDir/Jolson eso 6/19/00 hj
HFD-530/PM/Truffa/

cc:

Original IND _____ (SN 050, SN 060, and SN 062)
Division file
HFD-530/MO/Toerner
HFD-530/CSO/Truffa
HFD-530/cvetkovich
HFD-530/Jolson

Meeting Minutes (MM)
March 10, 2000

File: V:drive DAVDP/CSO/Truffa/IND/IND: _____/minutes/000310mm

**APPEARS THIS WAY
ON ORIGINAL**

Food and Drug Administration
Rockville MD 20857

IND _____

Hoffman-La Roche, Inc.
Attention: Cynthia Dillon
Program Director, CMC Regulatory Affairs
340 Kingsland Street
Nutley, New Jersey 07110

Dear Dr. Dillon:

Please refer to the meeting between representatives of your firm and the FDA on September 22, 2000. The purpose of this End of-Phase 2 Chemistry, Manufacturing, and Controls (CMC) meeting, was to obtain the Division of Antiviral Drug Product's concurrence and input on drug specifications, stability, comparability, and starting materials for your HIV-1 fusion inhibitor, T-20 (RO 29-9800).

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

Record of Industry Meeting

Meeting Date: September 22, 2000

IND: _____

Drug: T-20 (RO 29-9800)
HIV-1 Fusion Inhibitor

Indication: Treatment of HIV-1 Infection

Sponsor: Hoffmann-La Roche, Inc. and Trimeris

Type of Meeting: End of Phase 2 Chemistry, Manufacturing, and Controls,
(CMC Meeting)

FDA Attendees

Stephen Miller, Ph.D., Chemistry Team Leader, DAVDP
Rao Kambhampati, Ph.D., Chemistry Reviewer, DAVDP
Joseph Toerner, M.D., Medical Officer, DAVDP
Melissa Truffa, R.Ph., Regulatory Project Manager, DAVDP

External Constituents

Brian Bray, Ph.D., Director, Process Research and Development, Trimeris
Stanley Blum, Ph.D., Consultant, Quintiles/Trimeris
M.C. Kang, Ph.D., Vice President, Development, Trimeris
Carol Ohmstede, Ph.D., Manager, Strategic Planning, Trimeris
Sheila Whight, Senior Research Scientist, Trimeris

Robin Conrad, Program Director, Regulatory Affairs, Roche
Cynthia Dillon, Program Director, Regulatory Affairs, CMC, Roche
John Hakimi, Ph.D., Life Cycle Leader, Roche
Susanna Kevra, Ph.D., Global Supply Leader, Roche
Roger Micheli, Lead Analytical research/ Regulatory Affairs, Roche

Background

On June 14, 2000 (SN 073) the Sponsor requested an End of Phase 2 CMC meeting with the Division of Antiviral Drug Products to discuss a pre-meeting

briefing package that was submitted on August 24, 2000 (SN 082) that included questions for discussion.

Discussion

For each discussion topic, the sponsor's question is shown in regular font, followed by the Division's response in bold font.

Specifications

1. Provided in the briefing package is drug substance and product specifications that are currently in use and are proposed for Phase 3 clinical trials. Does the agency agree that the proposed specifications are adequate to support Phase 3 clinical trials?

The proposed specifications are adequate for the Phase 3 study. However, we have the following recommendations for the registration batches:

Drug Substance

a. [

b.]

Drug Product

a. []

Batch Analysis

a. []

2. Provided in this package are detailed descriptions of the manufacturing process and in-process controls in place for production of T-20 drug substance, would the agency consider a drug substance purity specification with a minimum of _____ acceptable for commercial manufacture?

We recommend that the sponsor increase the purity level of the final T-20 drug substance to _____

Stability

3. Outlined in this briefing package is a registration stability plan, including the drug substance and drug product stability data available to support the initial NDA filing scheduled for the first half of 2002, as well as possible stability amendments to be

submitted during the review period. Does the Agency agree with the registration stability plan outlined in this package?

Drug Substance: The proposed data for the primary site is acceptable. For the second drug substance manufacturing site, for at least _____ lot, provide _____ months of long-term and accelerated stability data by the midpoint of the review cycle. Alternately, release data for the validation lots at the second site can be provided instead of the site-specific stability data in the application. The validation data should be provided at least one month before the end of the review cycle. In either case please provide a commitment to place the first _____ lots from each site into the stability program.

Drug Product: The proposed data for the primary site is acceptable. For the second drug product manufacturing site, for at least _____ lot, provide _____ months of long-term and accelerated stability data at submission. Alternately, release data for the validation lots _____ can be provided instead of the site-specific stability data in the application. The validation data should be provided at least 1 month before the end of the review cycle. In either case please provide a commitment to place the first _____ lots from each site into the stability program.

Comparability

4. The plan for establishing comparable quality between drug substance manufactured at _____ manufacturing sites by the same process is provided in this document. Does the Agency agree with this comparability plan?

For comparability studies multiple batches from each site should be included.

Starting Materials

5. Does the Agency agree with the plan to classify the _____ for manufacture of each of the fragments as starting materials for the T-20 synthesis?

The designation of _____ as starting materials is acceptable.

Summary/Action Items

1. The Sponsor will continue to provide the Division with CMC data when available.
2. The Sponsor and the Division agree that the issue of purity can be discussed in future teleconferences.
3. The issue of drug stability and validation will require further discussions.

Minutes Preparer: _____ **Date:** _____

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

/s/

Tony DeCicco
9/25/01 12:35:36 PM

**APPEARS THIS WAY
ON ORIGINAL**



IND _____

Hoffmann-LaRoche, Inc.
Attention: Robin Conrad
Program Director, Regulatory Affairs
340 Kingsland Street
Nutley, New Jersey 07110

Dear Ms. Conrad:

Please refer to the meeting between representatives of your firm and FDA on September 29, 2000. The purpose of the meeting was to discuss key design elements of draft Phase 3 protocols for T-20.

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 Melissa M. Truffa, 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

Enclosure

**APPEARS THIS WAY
ON ORIGINAL**

Record of Industry Meeting

Date of Meeting: September 29, 2000

IND: _____

Drug: T-20

Indication: Treatment of HIV-1 infection

Sponsors: Hoffmann-La Roche Pharmaceuticals and Trimeris, Inc.

Type of Meeting: End of Phase 2 Meeting

FDA Attendees and Titles:

Division of Antiviral Drug Products (DAVDP)

Heidi Jolson, M.D., M.P.H., Division Director
Debra Birnkrant, M.D., Deputy Division Director, Clinical
Walla Dempsey, Ph.D., Deputy Division Director, Pre-Clinical
Therese Cvetkovich, M.D., Medical Team Leader
Joseph Toerner, M.D., Medical Officer
Narayana Battula, Ph.D., Microbiologist
Jeff Murray, M.D., Medical Team Leader
Kim Struble, PharmD, Clinical Reviewer
Teresa Wu, M.D., Medical Officer
David Morse, Ph.D., Pharmacologist
Jim Farrelly, Pharmacology Team Leader
Melissa Truffa, R.Ph., Regulatory Project Manager

Office of Clinical Pharmacology and Biopharmaceutics

Robert O. Kumi, Ph.D., Pharmacokinetics Reviewer, Division of Pharmaceutical Evaluation 3
Kellie Reynolds, PharmD., Pharmacokinetics Team Leader, Division of Pharmaceutical Evaluation 3

Division of Biometrics III

Tom Hammerstrom, Ph.D., Mathematical Statistician
Greg Soon, Ph.D., Mathematical Statistician

Division of Scientific Investigations

Antoine El-Hage, Ph.D., Branch Chief

External Constituent and Titles:

Trimeris, Inc.

Joan Drucker, M.D., Chief Medical Officer and Director of Clinical Trials

Sam Hopkins, Ph.D., Vice President, Medical Affairs

Carol Ohmstede, Ph.D., Manager, Strategic Planning

Prakash Sista, Ph.D., Clinical Virology and Pediatrics

Roche

Melanie Bishop, Regulatory Affairs (pediatrics)

Nick Cammack, Ph.D., Virology

Jain Chung, Ph.D., Biostatistician,

Robin Conrad, Program Director, Regulatory Affairs

Frank Duff, M.D., Clinical Science (pediatrics)

John Hakimi, Ph.D., Life Cycle Leader

Indra Patel, Ph.D., Clinical Pharmacologist

Miklos Salgo, M.D., Clinical Science Leader

Tom Steele, Ph.D., Non-Clinical Toxicologist

Background

The sponsor requested a meeting with the Division of Antiviral Drug Products (DAVDP) to discuss key design elements of draft Phase 3 protocols for T-20. A pre-meeting package was submitted (Serial number 086) that outlined the issues that the sponsor wished to discuss.

For each discussion topic, the sponsor's questions as outlined in the September 14, 2000 meeting package are shown in regular font, followed by DAVDP's response in bold font.

Discussion

Clinical Development Program (Adults)

1. Will the pharmacokinetic, safety, and efficacy data provided in this package support initiating the Phase 3 pivotal trials with a dose of 90 mg BID ~~intravenous~~ formulation administered as two injections per day?

We agree that 90 mg BID of the ~~intravenous~~ formulation will be the delivered dose for the Phase 3 pivotal trials.

2. Are the size and composition of the safety databases anticipated for NDA filing adequate?

In general, the number of subjects that will be included in the safety database appears to be adequate. In addition, we recommend that the sponsor plan to submit the required 180 day Safety Update about 60 days after the submission of the NDA. This safety update should include information from patients in the Phase 3 trials with longer term data (i.e. 9-12 months.) Timing for the submission of the Safety Update will be further discussed at a Pre-NDA meeting.

Questions 3 and 4 will be discussed together.

3. The durability of viral load suppression in the Phase 3 trials will be assessed at week 48 based on the results of two analyses for between-treatment comparison:
 - The percent of patients who maintained their 24-week virological response status (based on 3 mutually exclusive response categories defined in the protocols).
 - Average duration (in days) of first virological response (secondary analysis).
4. The described analyses will be sufficient to support a request for accelerated approval followed by a submission for traditional approval based upon surrogate endpoints.

The proposed 24 week endpoints have limitations, but we would find them acceptable, in particular given the *a priori* 0.5 log superiority of the T-20 arm over the control arm. In order to allow for a meaningful interpretation of the data in these open label studies, every effort should be made to maximize follow-up and minimize patient dropouts.

In previous discussions, we have expressed our concern about a 48-week “responder” analysis. We recommend that you include all study participants in the 48-week analysis and that a fourth response category defined as patients with lack of virological response be added. We believe that this type of analysis will result in less bias against the T-20 arm and that it would be a more appropriate analysis of the 48 week data used to support traditional approval. It was agreed that further discussions would be needed concerning this issue.

Additionally, we recommend that you use two consecutive viral load measurements to assess virologic failure criteria.

5. The sponsor requests any comments the Agency may have to the following:
 - Final Protocol T-20-301/NV16054:
 - Virologic failure criteria: We recommend that you utilize a two part virologic failure criteria.
 1. A decrease from baseline plasma HIV-1 RNA $< 0.5 \log_{10}$ on two consecutive measurements, starting at weeks six and eight or any time after week eight.
 2. A decrease from baseline plasma HIV-1 RNA $< 1.0 \log_{10}$ on two consecutive measurements, starting at weeks fourteen and sixteen or any time after week sixteen.
 - Statistical section: Please refer to our response to questions number three and four. In addition, with regard to the utilization of the last observation carried forward (LOCF), we would expect that in order to allow for a meaningful interpretation of the data in these open label studies, every effort should be made to maximize follow-up and minimize patient dropouts, and expect that an analysis that uses the LOCF will be robust to a sensitivity analysis. It should be noted that sensitivity analyses are not included in the product labeling.

- **Limited payment for Optimized Background (OB) regimen: Any means to keep all patients on assigned treatment will be paramount to the interpretability of this open label study.**
- **Adherence measures: The presentation today clarified that the assessment of adherence will include a determination of the presence or absence of protease inhibitors and/or non-nucleotide reverse transcriptase inhibitors in the serum.**
- **Metabolic sub-study: The proposed metabolic sub-study contains all the components usually recommended for metabolic studies.**
- **Sample informed consent. We recommend that you emphasize in the informed consent form that the procurement of OB will be the patient's responsibility, and that the patient notify the study coordinator immediately should their healthcare insurance and/or prescription coverage change.**
- **Patient self-injection video titled "The Patient's Guide to T-20: Learning the Process": Please emphasize that T-20 should be administered as a subcutaneous injection, not intramuscular. When available please include stability data on T-20 after reconstitution because longer-term stability data may enhance patient adherence.**
- **Roche Sample Repository (RSR) sub-study and consent: We requested that a discussion of this topic be postponed until a full protocol is submitted for review.**
- **Safety Reporting Plan:**
 - **Injection site form/grading system/method of collection: The proposed safety reporting plan appears to be acceptable. However, we recommend that you consider the inclusion of a sub-study that will address the clinical management of injection site reactions. The design of this study could be based on previous experience with management of injection site reactions.**
 - **Investigators will be asked to assign Adverse Event relationship as "Relationship to test drug (OB or OB plus T-20)" rather than assign relationship to individual drugs in the OB or OB + T-20 arm (For the OB = T-20 arm investigators will not be asked to assign relationship to T-20 versus the OB regimen). This proposal is acceptable. However, for serious adverse events (SAE) you should attempt to make a judgement about the relationship of the SAE to any of the medications the patient is receiving.**
- **Plans/Timing of an expanded access program. We encourage you to conduct an expanded access program but acknowledge that limitations in the manufacturing of T-20 may limit the number of patients that may be enrolled.**

Questions 6 and 7 will be discussed together.

Clinical Development Program (pediatrics)

6. Do the pharmacokinetic and safety data provided in this package support initiating the proposed pediatric program with a dose of 1.5 mg/kg?
7. The following pediatric data would be submitted at the time of NDA filing:
 - Single and multiple dose pharmacokinetic data on 12 children (3-12 years) and 12 adolescents (12-16 years)
 - 24-week safety and efficacy data for 12 children aged 3 –12 years (T-20-204/~~1005~~)
 - Preliminary snapshot of available safety and efficacy data from all ongoing Phase 1 and 2 trials at the time of NDA submission (approximately 70 patients from all 3 age groups), with additional high level safety data from the pediatric expanded access program, and single and multiple dose pharmacokinetic data on up to 12 infants (6 months – 3 years) assuming these children can be identified through existing pediatric research networks.

The selection of 1.5 mg/kg/dose for the proposed pediatric program appears to be acceptable. Further discussion of the adequacy of the pharmacokinetic data to support the proposed dose will occur after we have reviewed the actual data.

In general, the number of pediatric patients proposed appears to be acceptable for NDA filing based on preliminary information available for review. We would also recommend you include a broad range of age groups in your open label safety study.

8. The sponsor requests a waiver from the Agency on the requirements to study T-20 in ~~_____~~

[]

[]

Elements of the Proposed Clinical Pharmacology/Pharmacokinetics Plan

1. Is the clinical pharmacologic/pharmacokinetic plan adequate to assess the pharmacologic/pharmacokinetic parameters of T-20?

In general, we agree with your proposed clinical pharmacology/pharmacokinetics plan. However, we will need to receive complete protocols for review and future comment.

2. Are the drug interaction studies outlined in this package adequate to confirm that T-20 has minimal drug interaction potential? Would it be appropriate to conduct these interaction studies in parallel with the Phase 3 studies because of the minimal drug interaction potential?

In general, we agree with your proposed clinical pharmacology/pharmacokinetics plan. However, we will need to receive complete protocols for review and future comment.

3. The sponsor proposes to perform population pharmacokinetic analysis using NONMEM software to evaluate the influence of demographic factors on the pharmacokinetic variability.

A complete package with your plans for performing population pharmacokinetic analysis using NONMEM software to evaluate the influence of demographic factors on the pharmacokinetic variability needs to be submitted.

The sponsor indicated that they plan to submit a package outlining their plans for the population pharmacokinetic analysis in the near future.

4. The sponsor proposed that it is inappropriate to perform a radioactivity study in HIV-infected patients.

The omission of this radioactivity study in HIV-infected patients is acceptable.

5. The sponsor proposes that there is no need to perform studies examining the influence of renal and hepatic impairment on the pharmacokinetic of T-20 since T-20 is expected to be catabolised, by established pathways responsible for catabolism of proteins and peptides, into smaller peptide fragments and its component amino acids. However, the sponsor will evaluate the influence of renal impairment on the pharmacokinetics of T-20 in the population pharmacokinetic analysis.

This proposal is acceptable.

Questions 1-5 will be discussed together.

Nonclinical and Clinical Virology

1. Is the nonclinical and clinical virology program outlined in this document adequate to assess the virologic characteristics of T-20?

In general, the proposed nonclinical and clinical virology program is acceptable.

2. The sponsor proposes to use the _____ for the quantitation of HIV-1 viral RNA in studies T-20-301 and T-20-302 since this test kit is believed to be more sensitive for detection and quantitation of non-clade B virus isolates and is commercially available in Europe.

Please note that the _____ for the quantitation of HIV-1 viral RNA is investigational at this time.

3. The sponsor proposes to use the _____ assays for studies T20-301 and T20-302 despite the possibility that a percentage of patients with non-clade B viruses may not have resistance data (RTIs and PIs) available to help guide the selection of the background regimen.

The proposed assays for _____ are experimental, and they evaluate only a proportion of the HIV-1 genome. The usefulness of these assays in guiding the selection of background regimens and/or clinical outcome has not been demonstrated.

4. The sponsor proposes to defer the evaluation of patient-specific plasma virus phenotype for T-20 until a validated _____ assay is developed by any one of several vendors. In the event that a validated _____ assay is not available by 3 Q 2001, the sponsor proposes to analyze the T-20 phenotype sensitivity by using the _____ technique to isolate and evaluate PBMC virus.

This proposal is acceptable.

5. Resistance testing for investigational agents allowed in the phase 3 protocols is not commercially available. For consistency, the Phase 3 studies assignment of "approved" or "investigational" status will be based on a product's status within the United States at the start of study T20-301 (irrespective if the product's status in any individual country). The sponsor proposes that agents considered approved or investigational in the United States as of September 29, 2000 will be considered approved or investigational for duration of both trials, even if the agent and/or its corresponding resistance test becomes commercially available in the country in which the patient is treated (patients will be stratified by use or non-use of investigational agents).

This proposal is acceptable.

Elements of the Proposed Nonclinical Drug Safety Package

1. Is the nonclinical drug safety package outlined in this briefing document adequate to support the Phase 3 clinical investigations?

In general, the proposed nonclinical drug safety package is acceptable.

2. The sponsor has submitted a request to waive the carcinogenicity testing requirements for T-20 (S-081 dated September 6, 2000). If the CAC determine upon review that carcinogenicity testing is required for T-20, the sponsor proposes that NDA filing and approval should not be dependant on completion of animal carcinogenicity.

Currently, an unclear policy exists within the Agency concerning carcinogenicity testing. We recommend that you submit a briefing document that includes but is not limited to your rationale for requesting a waiver, genotoxicity information, and injection site reaction data that will be forward to the Executive CAC for review. This committee will make a determination based on the submitted information for T-20.

The sponsor indicated that this information had been included in the September 6, 2000 submission (S-081). **The Division agreed to review this submission and contact the sponsor if additional information was needed before presenting it to the Executive CAC for review.**

Other Discussions

1. The Division asked the sponsor if the development of antibodies to T-20 would be evaluated in studies T20-301 and T20-302. The sponsor indicated that antibodies to gp41 would be collected.
2. **Clinical Pharmacology/Pharmacokinetics/Absorption Site Variability:** We recommend that the absorption site variability of T-20 when injected at different body sites be evaluated to identify potential differences in T-20 absorption patterns. It would be useful to know if one particular site of injection is less favorable for T-20 absorption versus other sites studied.

Action Item

1. The Division's pharmacokinetic reviewer requested the assay validation report for T-20. The sponsor indicated that the assay validation report may have been previously submitted and would provide the project manager with the serial number for the appropriate submission. The sponsor also indicated that they would submit the validation report if it had not been submitted.

**APPEARS THIS WAY
ON ORIGINAL**

/s/

Tony DeCicco
4/5/01 09:52:15 AM
IND

APPEARS THIS WAY
ON ORIGINAL



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

IND _____

Hoffman-La Roche, Inc.
Attention: Cynthia Dillon
Program Director, CMC Regulatory Affairs
340 Kingsland Street
Nutley, New Jersey 07110

Dear Ms. Dillon:

Please refer to the meeting between representatives of your firm and the FDA on June 11, 2002. The purpose of this Pre-NDA Chemistry, Manufacturing, and Controls (CMC) meeting, was to obtain the Division of Antiviral Drug Product's (DAVDP) feedback on plans central to the preparation of CMC section of Roche's proposed New Drug Application (NDA) for T-20 (enfuvirtide) Lyophilized Vials (RO 29-9800).

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. Virginia Yoerg, 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

**APPEARS THIS WAY
ON ORIGINAL**



Record of Industry Meeting

Meeting Date: June 11, 2002

IND: _____

Drug: T-20 (RO 29-9800)
HIV-1 Fusion Inhibitor

Indication: Treatment of HIV-1 Infection

Sponsor: Hoffmann-La Roche, Inc. and Trimeris

Type of Meeting: Pre-NDA Chemistry, Manufacturing, and Controls, (CMC Meeting)

FDA Attendees

Bonnie Dunn, Ph.D., Supervisory Chemist
Stephen P. Miller, Ph.D., Chemistry Team Leader, DAVDP
Rao V. Kambhampati, Ph.D., Chemistry Reviewer, DAVDP
Steven Gitterman, M.D., Ph.D., Medical Team Leader, DAVDP
Melisse S. Baylor, M.D., Medical Officer, DAVDP
William H. Taylor, Ph.D., Pharmacologist, DAVDP
Karen A. Young, RN, BSN, Regulatory Project Manager, DAVDP

Hoffman-La Roche Attendees

Ms. Robin Conrad, Director, Drug Regulatory Affairs
Ms. Cynthia Dillon, Director, Regulatory Affairs, CMC
Dr. Armin Klein, Technical Registration
Dr. John Hakimi, T-20 Global Life Cycle Leader
Dr. Susanna Kevra, T-20 Technical Leader
Dr. Roger Micheli, Head, Analytical Research and Regulatory Affairs
Ms. Annie Miesch, Drug Product Analytics
Dr. Tom Steele, Nonclinical Toxicologist

Trimeris Attendees

Dr. Brian Bray, Director, Process Research and Development
Dr. Carol Ohmstede, Director of Corporate Planning and Partnerships
Ms. Sheila Whight, Assistant Principal Investigator, Analytics
Dr. Marna Doucette, Director of Regulatory Affairs and Compliance

Background

On May 17, 2002 (SN 329) the Sponsor requested a Pre-NDA CMC meeting with the Division of Antiviral Drug Products to obtain feedback on the Sponsor's plans which are central to the preparation of the CMC section of Roche's proposed NDA for T-20 (enfuvirtide) Lyophilized Vials (Ro 29-9800). The Sponsor plans for a rolling NDA submission with the last submission on August 30, 2002. After the Division's review of the briefing package, we sent two telephone facsimiles dated June 6 and June 7, 2002 which provided comments and recommendations from the chemistry and pharmacokinetics review teams.

Discussion

In the CMC Pre-NDA briefing package (SN 329), the Sponsor submitted three meeting objectives. Both chemistry and pharmacology/toxicology issues were discussed during the meeting. Please note the Sponsor's objectives are shown in bold font. The Agency responses and additional discussions and agreements are in regular font.

Chemistry Objectives

- 1. Roche/Trimeris understand the drug substance and product specification limits will be fully reviewed as part of the NDA application. We request the Agency's concurrence on our proposed tests, which will assure product quality and provide routine quality control of the drug substance and product, and our approach to justify the specifications.**

Drug Substance:

The proposed tests for determining the identity, quality, and purity of the drug substance seem to be acceptable; however, the final determination will be based on the NDA review. The acceptance criteria (limits) for the purity and impurities and other attributes would be determined after a complete review of the NDA data.

In addition, the following issues were discussed regarding the specifications:

- The proposed NDA drug substance specifications for appearance (solution test) includes the following: _____
_____ The Agency recommended that the Sponsor make efforts to prepare the drug substance that is _____
_____. In response, the Sponsor agreed to include the following in the proposed NDA submission: _____
[]
- The Agency suggested that the Sponsor provide justification for not including a microbial limit test in the batch release specification. In addition, the Agency recommended that the Sponsor use the water activity measurements in the justification.
- The Agency suggested that the Sponsor continue its efforts _____
_____ in Phase IV.

- The proposed stability data would be adequate to support the room temperature storage of the T-20 drug product.
- Storage of the T-20 reconstituted solution at 2-8°C for up to 24 hours is acceptable.
- During the NDA review, the 24-month expiration-dating period will be considered for the commercial product if the submitted data are supportive.

Additional Discussions:

- The release data for the _____ batch will be available in September 2002 instead of the earlier projected date of August. The Agency suggested that the Sponsor submit this data in an amendment to the NDA.
- The "inspection ready" dates for all facilities and shut down period for _____ facility will be provided.
- Release data for _____ drug substance validation batches (Roche, Boulder) will be provided in September 2002.
- [_____]
- The NDA submission will be in a conventional (paper) form, a categorical exclusion from the EA requirement will be requested, and the method validation package will be included in the NDA. A CD-Rom will also be provided for the CMC section but the format of the software will be discussed with the Agency at a later date.
- The Agency agreed to review the vial and carton labels for the Sterile Water for Injection (SWFI) prior to the August 2002 submission date.

Pharmacology/Toxicology Discussions

The discussion concerned the Sponsor's proposed Specified Limits for impurities in initial marketing drug product lots, and how the Sponsor qualified drug substance batches to support those proposed limits.

- The Sponsor was asked to address the basis for comparing doses in animals with doses in humans. The Sponsor described why it made the dose comparison on body weight (mg/kg) basis. The Agency agreed that the argument could be made, but stated that the argument needs to be made in writing.
- The Sponsor agreed to respond to all the questions from the June 6, 2002 telephone facsimile in writing.

Summary/Action Items

1. The Division and the Sponsor will continue to have follow-up discussion of a limited drug launch.
2. The Sponsor will provide a written response to the pharmacology/toxicology comments sent via telephone facsimile dated June 7, 2002.
3. The Sponsor agreed to the pharmacokinetics' request to receive certain data submitted to the NDA in a tabular format.

Minutes Preparer: _____ **Date:** _____

**APPEARS THIS WAY
ON ORIGINAL**

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

/s/

Stephen Paul Miller
10/16/02 09:15:22 AM

**APPEARS THIS WAY
ON ORIGINAL**

Food and Drug Administration
Rockville MD 20857

IND _____

Hoffman-La Roche
Attention: Ms. Robin L. Conrad
Director, Drug Regulatory Affairs
340 Kingsland Street
Nutley, New Jersey 07110

Dear Ms. Conrad:

Please refer to the meeting between representatives of your firm and FDA on June 11, 2002. The purpose of this Clinical pre-NDA meeting was to review the primary safety and efficacy data on T-20 (enfuvirtide) from your pivotal phase III trials and receive comment from the Division. A secondary purpose of this meeting was to review your proposal as to the NDA format, content, and timing of NDA related activities.

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) 827-2376.

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

RECORD OF INDUSTRY MEETING

Date of Meeting: June 11, 2002

IND: _____

Drug: T-20 (enfuvirtide, Ro 29-9800)

Indication: Treatment of HIV-1 infection

Sponsor: Hoffmann-La Roche and Trimeris Inc.

Type of Meeting: Clinical Pre-NDA Meeting

FDA: Attendees

Mark J. Goldberger, M.D., M.P.H., Acting Office Director, ODEIV
Debra B. Birnkrant, M.D., Division Director, DAVDP
Jeffrey S. Murray, M.D., M.P.H., Deputy Director, DAVDP
Steven Gitterman, M.D., Medical Team Leader, DAVDP
Melisse S. Baylor, M.D., Medical Officer, DAVDP
Rao V. Kambhampati, Ph.D., Chemist, DAVDP
William H. Taylor, Ph.D., Pharmacologist, DAVDP
Arzu Selen, Ph.D., Deputy Director, DPE3
Robert O. Kumi, Ph.D., Pharmacokinetics Reviewer, DAVDP
Julian J. O'Rear, Ph.D., Microbiology Team Leader, DAVDP
Narayana Battula, Ph.D., Microbiologist, DAVDP
Greg Soon, Ph.D., Biometrics Team Leader, DAVDP
Thomas Hammerstrom, Ph.D., Mathematical Statistician
Laura Pincock, Pharm.D., Senior Regulatory Review Officer for HIV Drugs
Jean-Ah Choi, Lead Consumer Safety Officer, DDMAC
Antoine El-Hage, Ph.D., Branch Chief, Division of Scientific Investigations
David L. Roeder, M.S., Associate Director for Regulatory Affairs, ODEIV
Anthony W. DeCicco, R.Ph., Chief Project Manager, DAVDP
Jeff O'Neill, RN, ACRN, Regulatory Project Manager, DAVDP
Nitin Patel, R.Ph., Regulatory Project Manager, DAVDP
Karen A. Young, RN, BSN, Regulatory Project Manager, DAVDP

Hoffman-La Roche Attendees

Robin Conrad, Drug Regulatory Affairs
Jain Chung, Ph.D., Biostatistician
Patricia Delora, Clinical Science (pediatrics)
Frank Duff, M.D., Clinical Science (pediatrics)
John Hakimi, Ph.D., Project/Life Cycle Leader
A. Heather Knight-Trent, Pharm.D., Drug Regulatory Affairs
Indra H. Patel, Ph.D., Clinical Pharmacologist
Katrin Rupalla, Ph.D., Drug Regulatory Affairs
Miklos Salgo, M.D., Clinical Science Leader
Thomas Steele, Ph.D., Nonclinical Toxicologist

Trimeric Inc. Attendees

Carol Ohmstede, Ph.D., Vice President, Corporate Alliances and Project Planning
Marna Doucette, Director of Regulatory Affairs and Compliance
John Delehanty, Director of Clinical Trials
Claude Drobnes, M.D., Director of Clinical Operations and Drug Safety
Lei Fang, Ph.D., Biostatistician
Michael L. Greenberg, Ph.D., Director of Molecular Biology

Background

The Sponsor requested a pre-NDA meeting to review the primary safety and efficacy data from the two Phase III trials as well as to review the format, content and timing of NDA related activities. Hoffmann-La Roche, Inc. provided the Division with the following three separate briefing packages:

Part A, dated April 10, 2002 (S-305)

This submission included the summary of previous key agreements made between the Sponsor and the Division, a Gantt chart showing the overall timelines for the NDA filing, an overall content of NDA filing, and an overall summary of T-20 as well as the most recent investigator's brochure.

Part B, dated April 30, 2002 (S-317)

This submission included 24-week primary efficacy and safety data from the Sponsor's pivotal Phase III trial T-20-301 (NV 16054).

Part C, dated May 31, 2002 (S-341)

This submission included 24-week primary efficacy and safety data from the Sponsor's second pivotal Phase III trial, T-20-302/BV16052. In addition, the Sponsor included a consolidated list of questions covering all three briefing packages.

The Sponsor submitted a list of questions and points for discussion. Prior to the meeting, the Sponsor conveyed the following objectives for the Clinical pre-NDA meeting: 1) To review and receive feedback from the Division on the primary safety and efficacy data of T-20

(enfurtide) from pivotal phase III trials; and 2) To review and obtain the Division's feedback as to the NDA format, content, and timing of NDA related activities.

Discussion

Please note the Sponsor's questions are shown in regular font, followed by the FDA response in bold font.

Questions from Part A of Briefing Package

Clinical Pharmacology

1. The sponsor proposes to submit an interim report of study NP 16221 in the NDA and submit the completed NP 16221 (Pittsburgh Cocktail) study report with or before the safety update.

The Division finds your proposal to submit an interim report of Pittsburgh Cocktail study acceptable and encourages you to submit the report as soon as it is available.

2. The sponsor proposes to submit NP 16324 "A Study to Investigate the Influence of Saquinavir (Fortovase®) Combined with Minidose Ritonavir (Norvir®) on the Pharmacokinetics of T-20 in HIV-1 Infected Patients" during review, before or with the Safety Update.

The Division finds your proposal acceptable and encourages you to submit study NP 16324 results as soon as it is available.

3. Does the Division have any comments to the proposed content and format of section 6 of the NDA?

The Division finds the proposed content and format of section 6 of the NDA acceptable.

The Sponsor conveyed which studies would have electronic datasets and what programs we could expect. Since the Sponsor is planning a rolling NDA, the Division encouraged the Sponsor to clearly state the references to the report and to electronically submit datasets with the individual study reports if possible.

The Sponsor plans to submit a rolling NDA beginning the end of June with an anticipated review clock start date of August 30, 2002.

4. Does the Division have any comments to the proposed content and structure of the Human Pharmacokinetic and Bioavailability Summary?

The Division finds the proposed content and structure of the Human Pharmacokinetic Bioavailability Summary acceptable. The Division will send any comments on the content of the summary via telephone facsimile.

Clinical Safety and Efficacy in Adults

5. The Sponsor proposes that the size and composition of the safety database are adequate for filing.

The Division agrees that the size and composition of the safety database are adequate for filing. The Division requested clarification that the Sponsor will submit data from Study T-20-204, since the safety database table did not discuss Study T-20-204. The Sponsor plans to submit Study T-20-204 to the NDA.

6. The Sponsor proposes to use a clinical cut-off date of March 6, 2002 for inclusion of data from ongoing non-pivotal trials in the NDA (T20-210, T20-211, T20-304, T20-305 and T20-310).

The Division agrees with your clinical cut-off date of March 6, 2002 for inclusion of data from ongoing non-pivotal trials.

7. The Sponsor proposes to use a clinical cut-off date of July 31, 2002 for inclusion of data from ongoing trials in the Safety Update. Additionally we propose that the Safety Update will be available within 2 months of the official User Fee clock start.

We concur; however, in the event that the data does not come in within three months of the start of the Use Fee Clock, we may have to extend the review clock.

8. Does the Agency have any comments to the structure for the phase III study reports as shown in the study report TOC?

The Division finds the structure for the phase III study reports as outlined in the study report Table of Contents acceptable.

9. The Sponsor proposes that it is appropriate to pool data from the two pivotal Phase III trials for presentation in the Integrated Summary of Safety and the Integrated Summary of Efficacy as outlined in the High Level Summary Safety and High Level Summary Efficacy DRAMs.

The Division finds your proposal to pool data from the two pivotal Phase III trials for presentation in the ISS and the ISE acceptable as long as individual clinical study reports are also available for review.

10. The Sponsor proposes the following regarding the ISS:

- a) The structure will be as shown in the attached ISS TOC.

The Division finds your proposal for the ISS structure acceptable.

- b) The safety results from the Phase II studies (T20-205, T20-206, T20-208), pediatric studies (T20-204/P1005, T20-310/NV16056), and rollover studies (T20-210, T20-211) will be summarized separately in the ISS using either the results provided in the respective clinical study report or interim analysis conducted using a clinical cut-off date of March 6, 2002.

The Division finds your proposal to summarize the safety results from the Phase II studies and rollover studies separately in the ISS acceptable.

- c) Similar clinical adverse event preferred terms will be collapsed into a single "project-defined adverse event term" in order to provide a more clinically meaningful summarization of adverse events. These terms will not be collapsed across all adverse event displays, but will be in specific additional designated "collapsed" displays.

This is acceptable; however, please provide clear definitions of how the decisions for collapsing similar clinical adverse events are made.

- d) In studies T20-301 and T20-302, certain serious adverse events consisted of an association of multiple signs/symptoms that were temporally related. For example, thrombocytopenia with neutropenia and fever has been reported. To determine whether or not individual events may be associated, analyses will be performed to determine whether or not selected events or serious adverse events occurred concurrently.

The Division concurs; however, as for Items B & C, the basis/rules for making these determinations must be clear.

11. The Sponsor proposes the following regarding the ISE:

- a) The structure will be as shown in the attached ISE TOC.

The Division finds your proposal acceptable.

- b) The efficacy results from the Phase II studies (T20-205, T20-206, T20-208) and pediatric studies (T20-204/P1005, T20-310-NV16056) will be summarized separately in the ISE using either the results provided in the respective clinical study report or interim analysis conducted using a clinical cut-off date of March 6, 2002.

The Division finds your proposal to summarize the efficacy results from the Phase II studies separately in the ISE acceptable.

- c) Genotypic and Phenotypic Sensitivity Scores (GSS and PSS) will be assigned as described in the attached ISE DRAM and mean change from baseline over time for log₁₀ HIV-1 RNA and CD4+ T cells will be analyzed for GSS and PSS subpopulations.

The GSS and PSS scores are acceptable for use as only one part of the analyses of resistance. However, the Division does not anticipate the use of this data in any labeling.

- d) Planned subpopulation analyses provided for in the ISE, to be based on patient demographics, baseline characteristics, and ARVs in the OB regimen, may be considered for approval of T-20 in the event that results from T-20-301 and/or T20-302 are equivocal.

It is our impression that this question is no longer pertinent, since the results of Studies 301 and 302 are available. Of course, we are interested in seeing these subset analyses and additional subset analyses including degree of previous treatment and analyses by antibody level when available.

12. The T-20 pivotal studies were designed to use surrogate marker data (HIV-1 RNA) to allow accelerated approval based on 24-week data and full (traditional) approval based on durability of response shown with 48-week data; this will be pursued. Although the study is not powered to show a statistically significant benefit in clinical endpoints (AIDS defining events and deaths) the sponsor proposes that in the event that there is such a benefit demonstrated by the 24- or 48- week data (balanced for exposure), this outcome could be considered for traditional approval.

The Division concurs. Examination of the data at week 24 and at week 48 for traditional approval constitutes two looks; therefore, multiple comparison adjustment is needed. Unless otherwise stated in the original study protocol, we will use a p value of 0.001 as the standard at week 24.

13. Does the Agency have any comment on the content and format of section 8/10 of the NDA?

The Division does not have any comments on the content and format of sections 8 and 10 of the NDA.

Pediatrics

14. The Sponsor proposes that the data to be provided will support inclusion of a pediatric dosing recommendation for children and adolescents from — through 16 years of age in the eventual package insert.

Pediatric information that is included in the label can only be decided after reviewing the data.

The Sponsor requested clarification on a telephone facsimile sent by the Division on June 7, 2002.

15. The Sponsor proposes that the eventual package insert will also contain pediatric information in the PK and Pediatric Use sections.

Again, this is a review issue.

Patient Education

16. The Sponsor proposes that the patient education plan provide for the core critical materials necessary to ensure successful patient training and support. Does the Agency have feedback or comments on the materials listed?

The Division strongly believes that a good patient education program is vital for the safe and successful launch of T-20. The Division and Sponsor agreed to work closely together and to include other Divisions within the Agency, such as the Division of Surveillance, Research, and Communication Support (DSRCS) and the Division of Drug Risk Evaluation (formerly DDMAC).

The Division asked specific questions as to how physicians will receive patient starter kits and what educational materials and injection supplies will be provided to the patient.

As previously discussed, once the patient education materials are available, the Division would welcome a face-to-face meeting to discuss your patient education plan in detail. The Sponsor anticipates that the first mock-ups will be available around the end of June. At that time, a meeting between the Sponsor and the Division will be scheduled, tentatively after July 15, 2002.

Since the approval of promotional products requires 1 – 3 months to review, the DDRE reminded that the Sponsor to send in proposed labeling as soon as possible.

17. The Sponsor proposes that the educational items identified need to be available at the time of launch. We plan to submit them shortly after NDA filing and would like to work with the Division and DDMAC to facilitate early approval of these pieces.

Since your application is being submitted under accelerated approval/subpart H, these patient education materials must be reviewed prior to launch. We request that you submit all materials as soon as possible so that the Division has plenty of time to review.

Questions Covering Parts B & C of Briefing Package

1. The Sponsor proposes that studies T20-301 and T-20-302 have met their primary endpoint and support filing and potential approval of T-20 for the treatment of HIV-1 infection. The sponsor solicits the Agency's comment with regard to the data from studies 301 and 302. A summary of the key efficacy and safety data from study T20-301 was included in Part B of the meeting briefing package.

We look forward to the review of Studies 301 and 302, but we cannot comment on Studies 301 and 302 without first reviewing them.

2. The Sponsor proposes that the data from studies T20-301 and T20-302 support priority review of T-20.

It is highly likely that the T-20 NDA will support a priority review. However, this decision will be made at the filing meeting. In your NDA submission, we would expect you to provide justification for a priority review.

3. The Sponsor requests the Agency's feedback with regard to the need for and potential timing of an advisory committee meeting for T-20.

We anticipate an advisory committee meeting approximately four months into the review clock. If the NDA were submitted as planned, we would anticipate an Advisory Committee Meeting would likely be in the first weeks of January 2003.

4. The Sponsor requests any other feedback the Agency may have with regard to the safety and efficacy data presented from study T20-301/T20-302, our filing plans or NDA related documents as outlined in Part A of the briefing package.

At this time, the Division does not have any comments regarding the safety and efficacy from Studies 301 and 302; however, questions may arise during the review.