

FUZEON BRAND ENFUVIRTIDE (T-20)

Breaking barriers or breaking the bank?

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**for the Treatment Action Group (TAG)
and other endorsing community organizations and individuals (list below)**

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1. Introduction

Research and advocacy have brought forth 16 approved antiviral medications targeting two different stages in the HIV lifecycle. These drugs, when used in potent combinations, have significantly reduced morbidity and mortality in people living with HIV. However, for the large number of people who have been treated for years and have developed drug-resistant viral strains, the present drugs are often insufficient to achieve durable viral control. Because HIV rapidly evolves resistance and cross-resistance to available drugs, there is a clear need for therapies that target other points in the HIV lifecycle.

T-20 is the first drug of a new class of HIV inhibitors that perform entry inhibition. More specifically, T-20 is one of a subset of entry blockers called fusion inhibitors. It acts by preventing the envelope of HIV from fusing to its target's cellular membrane. For treatment experienced individuals with multiple-drug resistant virus, adding a drug from a new inhibitor class in combination with drugs from previously used classes is thought to be the most effective strategy for achieving durable viral suppression. As with all other HIV therapies, T-20 must be used in a combination, preferably with other new agents, in order to have the biggest punch.

T-20 has been shown to be active *in vitro* against virus using either CXCR4 or CXCR5 co-receptors, or both. Its mechanism of action occurs outside of the cell wall, and the drug does not appear to penetrate cells to any significant extent. Therefore T-20 is not expected to disrupt intracellular metabolic pathways or stimulate intracellular destruction.

Initially developed by Trimeris, Inc., since 1999, F. Hoffmann-La Roche and Trimeris (Roche/Trimeris, the sponsor) have collaborated on the development and production of commercial quantities of T-20. Both companies will market the drug within the U.S. and Canada, and Roche will solely market the drug in the rest of the world. It is hoped T-20 will be licensed for commercial sale and will be in U.S. pharmacies by the second quarter of 2003.

It is high time that a new HIV drug class becomes available. Based on positive results from two large phase III pivotal studies, Roche/Trimeris have submitted an application to the Federal Food and Drug Administration (FDA) for final approval and the FDA has granted priority review status.

Based on data from ongoing and completed studies, TAG believes that the Roche/Trimeris application for accelerated approval of Fuzeon brand enfuvirtide

to treat HIV infection in combination with other antiretroviral agents in adults and adolescents should be approved by the FDA.* FDA should ensure that Roche/Trimeris advertising materials specify that the drug has only been studied in heavily pretreated individuals with low CD4 counts (in the Phase III TORO 1 and TORO 2 studies).

2. Overview of Issues

Although therapeutically promising, unfortunately T-20 is not an easy drug to use and may be difficult for some to access.

Its drawbacks include:

- 1) The requirement that T-20 be injected twice daily,
- 2) A high incidence of problematic (painful and persistent) injection site reactions (PISRs),
- 3) Complex and lengthy reconstitution of each dose,
- 4) Inadequate drug supply, and
- 5) High price.

Twice daily injection

Because it is a complex protein peptide, T-20 has to be administered by subcutaneous (subQ) injection twice daily, a substantial issue for most people. Adherence to life-long oral HIV therapies is already inherently difficult. The technical demands of self-administering a twice-daily injectable drug are even more so, and we find the Roche/Trimeris video of people effortlessly incorporating T-20 into their daily lives misleading. Interestingly, the T-20 educational plans do not take into account the difficulties outlined below and how people can deal with them. A specific program is needed to deal with the complexity of drug reconstitution and self-injection. Patient experience may be very helpful in elucidating some basic dos and don'ts. Fuzeon has challenges in common with other injectable drugs, including the significant concerns many former injection drug users in recovery have regarding any use of needles as a potential trigger for relapse.

Problematic Injection Site Reactions (PISRs)

The Achilles heel of T-20 may be the ISR's. T-20 injections cause a local, painful skin reaction, somewhat like a wasp sting, in almost all (98%) people studied thus far. Many people, especially users of T-20, are frustrated with the lack of importance given to this issue by the sponsor. Because both the cause and the resolution of these may be key to success on this drug, we will be using the term PISR (problematic injection site reactions) in this paper, not the sponsor term ISR. Roche/Trimeris needs to learn more about why these PISRs occur and must look into other delivery mechanisms for the compound. Besides PISRs, T-20 has side effects (grade 3 and up, in less than 10% of people) of nausea and vomiting, neutropenia, anemia, and elevated SGPT and amylase.

*A large minority of the community present at an ATAC strategy session at the 10th CROI voiced opposition to T-20 accelerated approval, based on a number of key scientific points as

well as overarching feelings of frustration. Never has one drug had such an ominous ripple effect.

Reconstitution

The unreconstituted drug can be maintained out of the refrigerator. Reconstitution is the first drawback to ease of use. After mixing the sterile water with the powder, T-20 can take up thirty minutes or longer to dissolve completely. It is unclear whether total reconstitution is necessary for efficacy. Often the solution is drawn up in the needle before the drug is completely dissolved. What is “completely” dissolved? Is injection of unreconstituted substance contributing to PISRs? Although waiting for the drug to reconstitute is another barrier to efficient delivery, recently it has been shown that a reconstituted vial, if not used immediately, can be stored in the refrigerator for up to 24 hours. Consequently it is possible to reconstitute 2 vials simultaneously and place one in the refrigerator. In this way the stored vial, once brought back to room temperature, could be used without the need to wait for reconstitution. This practice allows people to reconstitute their second vial along with the first, cutting the daily waiting time for this step in half.

Supply

Fuzeon is reported to be the most difficult HIV drug heretofore manufactured. It is a complicated protein requiring at least 106 steps to produce and is dependent on large quantities of processed materials supplied by third parties. Trimeris, the originator and designer of T-20, entered into partnership with Roche in order to manufacture the complicated peptide. According to the sponsor, the commercial manufacture of T-20 is the first time that synthetic peptides have been produced at this scale. Once the companies believed they had a worthwhile product, they scaled up production by designing a new, specialized production plant in Colorado. However, difficulties in developing production capacity and acquiring raw materials have limited drug supply and have held back implementing the expanded access program. Until the new plant came on-line, small-scale production had only been able to meet the needs of clinical trials and a small expanded access program (1200 slots world-wide that took an excessive six months to enroll). Full-scale production for marketing had been promised to be up and running without hitches by the beginning of 2003. But after reports that only half the amount hoped for would be available at time of launch, a limited initial distribution plan has been developed.

Producing enough T-20 for all the research, the expanded access program and expected market demand has been a major stumbling block in the development of this drug. Because of the production difficulties, and the fact that a drug of this complexity has never been produced before, there is no promise that enough drug can be produced in a timely manner to reliably supply all who need it. The sponsor is reserving a 5 month supply for every patient who begins therapy with T-20. This plan is heartening, although it may be contributing to the astronomical price.

Price

A wholesale price of \$20,440 has been announced for the European market. Although there had been rumors and pre-emptive justification of a high price, this drug is showing us that there need not be relationship between price and efficacy. Is this the drug that will break payers' backs? Will providers be unable to justify or afford the high cost and refuse to add T-20 to their formularies, despite patient need?

3. The Community Demands

Commit to informed access

An aggressive commitment to patient and provider education will be required as the number of people using T-20 swells from 2000 to perhaps 15,000 by year's end. Up to now, the sponsor has not shown itself ready, willing, or able to do this. Education, for both the user and provider, must be the top priority on the Roche/Trimeris agenda and the *educational program* must be set up and in place at the time of approval.

Minimize barriers to adherence

Toxicity management issues need to be better studied. Health care providers and patients need to understand the *time commitment* required to use T-20 correctly to be more comfortable prescribing it and obtaining the best advantage from its use. *Treatment fatigue* is common with oral HIV treatments. The desire to "skip" one dose per month (a fairly common occurrence even with oral meds) may be more risky in heavily pretreated people.

Quality of life issues resulting from the use of *injectable drugs* remain problematic. The trend in HIV treatment is towards drugs that are simpler to use. T-20 bucks this trend. *Adherence issues* and *PISRs* must be dealt with aggressively by the company, with more scientific research, studies into different ways to administer the drug, and careful clinical programs to *counsel people* on the best, safest methods of injection in order to make T-20 more user friendly. It is important that T-20 not join a person's list of quickly "used up" therapies. The FDA should recommend a *patient/health care provider advisory board* to work on these issues.

Get to the bottom of PISRs

According to data from the sponsor, PISRs occur in nearly all who use T-20 and have been the major adverse event in all studies to date. Fifty percent are reported as mild, while the other 50% are between moderate and severe. *Erythema* (of more than 4") and pain have been reported in 80% of people and *induration of 2"* in 85% of people. 20% of the PISR nodules do not go away even after 7 days. There does not seem to be improvement over time.

PISRs may be caused by injecting too close to the skin, which people may do to avoid the nodules. Others who inject "deeper" may be accumulating sub-derma scar tissue that also doesn't go away. Some insulin injectors have suggested to warm the syringe before injection. Also, the skin surface in general may harden as surface scar tissue.

In a poster at CROI 2003, in an analysis of the pathology of the (P)ISRs, one of the results was that the single patient (out of seven studied) who did not have (P)ISRs “had insulin-dependent diabetes and had self-injected insulin for many years using optimum injection techniques, according to various healthcare providers associated with the patient.” Are PISRs nothing more than bad injections? If so, the sponsors’ education plan has not worked. Easier modes of delivery need to be looked into. If it is something else (allergy, etc.), then that needs to be clarified. Does the incomplete dissolution of T-20 have anything to do with the PISRs? Is there a point when, although not completely dissolved, it is safe and efficacious to use?

Continue dosing research

Questions have been raised concerning the potency of the control regimen and the small sample size used in the Phase II study T20-206. Trimeris never ascertained the maximum tolerated dose for T-20 and based its dosing decision solely on the tolerability of the number of injections, as well as on the viability of maintaining adequate drug levels at that dosing schedule. While it was relatively easy for people on the approved sub-optimal dose of saquinavir to double the dose, that will not be possible with T-20. Roche/Trimeris should continue to look for the maximum tolerated dose, which will mean more investigation into delivery systems.

Help identify optimal background regimens

In multi-drug experienced people, therapy optimization should be ascertained via genotyping or, when appropriate, phenotyping. The recent news that only 25% of practicing clinicians know how to use the results of these resistance tests is very disconcerting. T-20’s label needs to specifically mention continuing medical education (CME), etc. A clear understanding and reading of the resistance results would allow for an individualized optimization of the background therapy, and thus improved response.

Guarantee Access to those who need it most

With only a 16% success rate for binging viral load < 50 copies/mL in the heavily pre-treated trial participants, and with drug supply limited, this drug may need to be rationed to those most in need -- those without other treatment options. Use in other populations has not been studied, and the risk-benefit ratio in a treatment-naive population has yet to be determined. Finally, it should be noted that there are no study results demonstrating the impact of T-20 on the clinical progression of HIV disease.

When the expanded access program was being planned, activists demanded that it enlist people equitably and from as many diverse populations as possible. The community was assured that new and different investigators would be chosen by the company to ensure that the drug was offered to people who typically were left out of such access programs, and to ensure that those needing a salvage therapy would receive T-20. Unfortunately, as with most expanded access programs to date, the sponsor delivered “too little, too late.” The program has only recently begun providing significant amounts of drug even as final FDA approval is days away. This timing has

allowed little access to the drug outside of clinical trials. T-20 has been studied primarily in a pre-treated population, in adults who are multi-therapy experienced, with multi-resistance and limited treatment options. This population; i.e., those most in need, must be guaranteed continued first access to this drug, regardless of the ultimate label indication approved by the FDA.

Assure equitable access

Roche/Trimeris must assure that scaled-up production will be able to meet demand with no further supply issues. Roche/Trimeris must ensure that there is an adequate supply of the drug for continued clinical trials, expanded access, and for sale throughout the world. They must show that it is possible within reason to meet patient demand, and work to avoid anticipated access problems that may arise. Because 25% of the Phase III trials took place in Brazil, it is fair that the sponsor guarantee a proportionate share of drug to Brazil, as soon as it is available. Sufficient drug to conduct Phase IV studies of treatment options and side effects should be assured.

There will be a maximum of 15,000 T-20 slots available in 2003. Roche/Trimeris need to come to reasonable terms over its price with all payers, whether they be insurance companies, Medicaid or ADAPs. Details of the sponsor's "Patient Assistance Plan" (PAP) need to be defined (Roche has verbally promised 1/3 of drug to those most medically needy). The entry criteria for the PAP may well be determined by those who are unable to enter state ADAP plans. Administration of PAP eligibility should be coordinated with the ADAPs.

Tell the truth

The FDA needs to take its role as monitor of pharmaceutical advertising very seriously and remember that the wording in the label and advertising for the use of this drug should not be ambiguous or misleading regarding target populations. The FDA should insist that those people most likely to benefit from T-20 have first access.

4. Post-marketing research

The community also demands that, within the constraints of existing law, the FDA mandate that Phase IV (follow-up) studies of unresolved questions listed below be designed and initiated within one year.

1. How can heavily pre-treated people resistant to all three current classes of antiretrovirals maximize the benefits of T-20?
2. Intensive study of biological interactions is needed:
 - Does gp41 blocking prevent the cell from performing another as yet unknown function?
 - Fifty percent of people develop antibodies to T-20 at six months. What are the clinical and virological consequences of this, and does antibody binding reduce bioavailability?
 - The creation of gp41 antibodies has always been a major fusion hurdle, yet the Roche poster says that in 50% of those analyzed in a small study,

- no antibody response was seen. Might this become clinically relevant over a longer period of time in more people?
- Is chronic inflammation response an issue?
 - The inflammatory response may be exacerbated in people who already have asthma and/or dermatitis. This needs to be carefully characterized.
 - Is the 10% eosinophilia clinically relevant? Or is it signaling an allergic response? It is not known if this is related to hypersensitivity, of which there have been 3 cases, one attributable to abacavir, the other two to T-20, one of whom died.
 - Hypersensitivity needs to be better defined, monitoring guidelines need to be developed, and predictors of hypersensitivity such as HLA type need to be explored. Probably the easiest way to conduct post marketing toxicity follow-up would be through an intensive open-label program.
3. A long-term toxicity management study needs to be done, especially in relation to the PISRs. This should investigate topical pain relievers (ointments, etc) and the massage techniques many people are using in order to make the PISRs more manageable. What (if any) topical analgesics are safe (steroidal, non-steroidal, etc) and how should they be applied? For individuals with lipoatrophy there may be less superficial fat. In these cases, where does one inject?
 4. TORO 2 showed once again that two new classes are better than one (or in this case, 1.6 drugs are better than one). The sponsor must commit 10% of the total amount of T-20 manufactured to study combinations with promising new drugs like tipranavir, tenofovir DF, atazanavir, fosamprenavir, or any new drugs active against drug-resistant HIV, so that people can get the biggest bang for the bucks that T-20 is asking. These multi-experimental agent studies must begin now.
 5. A study of the efficacy of intermittent use of T-20 would be helpful. Possibly one way to assist longer-term adherence would be to offer clinically directed partial or intermittent interruptions, based on CD4 and HIV RNA as markers. Occasional breaks may allow a person to better tolerate and adhere to this difficult treatment, possibly avoiding treatment failure due to adherence fatigue. Could T-20 be used as a treatment stabilizer (having an indication even though only partial viral suppression is achieved)?
 6. Using an injectable drug in children has serious implications for adherence and may cause distress in children who fear needles. Larger pediatric studies need to be performed and care should be taken in looking at quality of life with use of T-20 in children.
 7. A first report from a drug-drug interaction study was presented at CROI 2003, but more needs to be done. Why would ritonavir cause a 34% rise in AUC, yet prior lopinavir/r use be associated with a reduced virologic response? More interaction studies need to be done, including studies with methadone, contraceptives, and the most popular PI, nelfinavir.
 8. A study of T-1249 in T-20 treatment failures needs to be done. How many people, and who exactly, can use T-1249 after the failure of T-20? Do accumulated T-20 mutations eventually cause resistance to T-1249?

Both TORO studies are to continue to 48 weeks for full approval of T-20. The HIV Community asks that TORO 1 and TORO 2 be amplified and include other experimental agents. Then, background treatments could be stratified and analyzed. Also, the mechanisms of toxicity issues like PISRs, the inflammatory response, the eosinophilia and the hypersensitivity reaction, and how to either avoid them or respond to them, could be amended into the TOROs.

We support the accelerated approval of Fuzeon (aka, T-20) and look forward to its equitable availability, but more research is needed to insure that those who need it most will receive the full benefit, with minimal impact on quality of life.

This Position Statement is endorsed by the following organizations and individuals:

ACT UP/NY

AIDS Survival Project, Atlanta

AIDS Treatment Activists Coalition (ATAC), USA

AIDS Treatment Data Network, NY

AIDS Action Baltimore

AIDS Treatment Activist Coalition (ATAC), USA

The Center for AIDS: Hope & Remembrance Project, Houston

Canadian Treatment Action Council (CTAC)

CHAMP (Community HIV/AIDS Mobilization for Power), Philadelphia

Gay Men's Health Crisis, NY

Save ADAP, USA

(We are: Organizations: ACT UP Philadelphia, AIDS Action Baltimore, AIDS Foundation of Chicago, AIDS Treatment Data Network, Florida AIDS Action, International Foundation for Alternative Research in AIDS, Project Inform, Title II Community AIDS National Network. Individuals: Jim Musslewhite, Olympia, WA; Susan Gibson, Texas; Doug Rose, Baltimore, MD; Mark Peterson, Detroit, MI)

National AIDS Treatment Advocacy Project (NATAP), New York

Search For A Cure, Boston

Tennessee AIDS Support Services, Inc. (TASSI)

Test Positive Aware, Chicago

Fred Schaich, Los Angeles

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Cathy Olufs, Los Angeles
Melvin Littles, NY

For more information, please contact Rob Camp at Treatment Action Group at 1.212.253.7922. A longer version of this Position Paper, including a summary of the scientific data, can be found at <http://www.aidsinfonyc.org/tag/index.html>

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