Clinical Review Cover Sheet

NDA: 21-481

Sponsor: Hoffman-La Roche, Inc.

Drug name: Fuzeon (enfuvirtide, T-20)

Reviewer: Melisse Baylor, M.D.
                      Division of Antiviral Drug Products

Documents reviewed: 1. Original New Drug Application submitted September 16, 2002
2. Safety Update Report submitted November 15, 2002
3. Additional information submitted January 29, 30, 31 and
February 3, 4, 5, 6, 7, 10 and 14, 2003

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Clinical Review for NDA 21-481

Executive Summary

I.   Recommendations

A.   Recommendation on Approvability

Decreases in morbidity and mortality are observed in HIV-infected patients treated with highly active antiretroviral therapy (HAART). Successful antiretroviral regimens usually require three or more drugs. Treatment with HAART reproducibly yields improvements in immunological and virological biomarkers that correlate with clinical improvement. Changes in these surrogate markers are accepted by FDA as a necessary basis for the approval of new antiretroviral therapy.

Unfortunately, HIV resistance to antiretroviral therapy frequently develops during treatment and may be complicated by cross-resistance to other agents in the same drug class. Because of widespread viral resistance and because of significant toxicity associated with many of the currently approved drugs, there is an urgent need for new antiretroviral drugs. This is particularly true for drugs with patterns of resistance different from currently approved agents. New classes of antiretroviral agents with different molecular targets offer the promise of activity against drug resistant HIV, as well as potentially more favorable toxicity profiles than existing antiretroviral therapy.

Fuzeon (Enfuvirtide, also known as T-20), is a 36 amino acid synthetic peptide that acts against HIV by interfering with the fusion of HIV to CD4 cells. Enfuvirtide is the first HIV entry inhibitor to be reviewed for approval in the United States. It is administered by subcutaneous injection twice daily. Fast Track status was granted in January 1998. NDA 21-481 was submitted for accelerated approval under 21CFR 314.500 (Subpart H-Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses) on September 16, 2002.

A total of 1013 subjects enrolled in two Phase 3 clinical trials of enfuvirtide and were randomized 2:1 to either enfuvirtide plus an 'optimized' antiretroviral background regimen (n=673) or to an 'optimized' background regimen alone (n=340). Decreases in circulating HIV and increases in CD4 cell counts were observed in the enfuvirtide arms of both Phase 3 studies at 24 weeks of treatment. Effects were statistically strong and robust: similar effect sizes were seen in all population subgroups analyzed. The effect size observed (a viral load decrease of approximately 0.85 log) is clinically meaningful, and has been accepted as a basis for approval for other antiretroviral agents.

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The most common adverse events associated with enfuvirtide use were local injection site reactions (ISRs), reported in 98% of subjects enrolled in Phase 3 clinical trials. Most subjects experienced pain, erythema, and induration at an enfuvirtide injection site. Most subjects continued treatment with enfuvirtide despite these reactions; relatively few subjects (4%) discontinued therapy because of ISRs. Infectious complications at the injection site were uncommon, reported in approximately 1% of subjects

More severe but less common adverse events observed during clinical studies included hypersensitivity reactions, seen in less than 1% of subjects receiving enfuvirtide. Signs and symptoms of hypersensitivity reaction included fever, rash, nausea, vomiting, hypotension, and increased transaminases. Rare cases of immune complex disease, i.e., glomerulonephritis, and Guillain Barre Syndrome, were observed.

Both Phase 3 studies showed a relative increase in the incidence of bacterial pneumonia for subjects receiving enfuvirtide versus control subjects. However, the significance of this finding is uncertain. The increased risk seen in subjects randomized to enfuvirtide may have been partially due to the study design used in both Phase 3 studies, or possibly due to an atypically low incidence of pneumonia in the control (OB) arms. Regardless, as a member of a new drug class, an immunosuppressive effect of enfuvirtide cannot be excluded.

The magnitude of the antiviral effect observed in the Phase 3 trials warrants approval of enfuvirtide. This effect is comparable to the effect seen for other marketed antiretroviral agents originally approved on the basis of antiviral activity. It is felt that appropriate labeling and patient education will permit adequate risk management of potential hypersensitivity reactions. Although it is unclear at this time whether there is a true immunosuppressive effect of enfuvirtide, this potential adverse effect should also be manageable by appropriate patient and physician education. There are also concerns regarding the emergence of resistance to enfuvirtide in clinical practice. This is a known concern with the use of all antiretroviral medications, and is best managed by use of enfuvirtide only as part of an active combination regimen. It should not preclude approval.

Enfuvirtide is indicated in the package insert for subjects previously exposed to other antiretrovirals. The sponsor has developed extensive patient and professional educational materials to address the challenges faced by enfuvirtide, the first parenteral HIV therapy likely to be used widely. These materials will significantly enhance patient safety and permit the drug to be used safely in the targeted population. Approval of this agent is recommended.

B.   Recommendation on Phase 4 Studies and/or Risk Management Steps

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It is essential that patients initiating treatment with enfuvirtide be carefully educated how to self-administer drug. To address this, the applicant has developed extensive patient education materials to maximize patient safety, compliance, and convenience. Patient education materials include an injection instruction booklet, instructional videotape, a caregiver's brochure, and a patient package insert. In addition, the applicant will provide patients with a travel kit, a placemat surface (with instructions) for preparation of drug, and sharps containers to enhance both the safe use of enfuvirtide and the safe disposal of syringes. A website and a toll free number for patients who have questions about the use of enfuvirtide have also been established. All materials emphasize the need for health care providers to educate patients prior to initiating enfuvirtide therapy.

Phase 4 commitments are planned to further study possible immunosuppressive effects of enfuvirtide, which may have been manifest as the increased incidence of bacterial pneumonia in Phase 3 clinical trials. Phase 4 plans include a large clinical cohort study to further assess the risk of pneumonia associated with enfuvirtide use and additional preclinical studies to define if there is an increased risk of pneumonia in animal models. *In vitro* studies of possible mechanisms of enfuvirtide immunosuppression are also planned.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

Enfuvirtide is the first drug to be submitted for approval in the antiretroviral drug class of entry inhibitors. It prevents fusion of HIV-1 to the CD4 cell membrane thereby inhibiting the first stage of HIV infection of new cells. This mechanism is different from any other approved agent. It is administered as a subcutaneous injection. Enfuvirtide studies include three Phase 1 / 2 studies, three Phase 2 studies, five clinical pharmacology studies, three rollover studies, two pediatric studies, two Phase 3 clinical trials, and one open-label safety study. A total of 1541 subjects have received at least one dose of enfuvirtide. Of these, 1401 received enfuvirtide at the dose proposed for labeling (90 mg bid in adults and 2.0 mg/kg for children aged 6 years and older). Nine hundred and thirteen of the 1541 subjects have received enfuvirtide for at least 24 weeks, and 569 subjects have received enfuvirtide for at least 48 weeks. Of the studies submitted, the two randomized, controlled, Phase 3 studies (n = 1013) are considered most important for this submission. Subjects studied in these trials were heavily pretreated patients with persistent viremia despite ongoing treatment with combination antiretroviral therapy.

B. Efficacy

Enfuvirtide was studied in two Phase 3 clinical trials: study T20-301 enrolled 501 subjects at 48 sites in North America and Brazil, and study T20-302 enrolled 512 subjects at 67 sites in Western Europe and Australia. These studies were almost identical in design. Primary entry criteria were: (1) previous experience with ARV therapy from all three approved antiretroviral classes, defined as treatment with one nucleoside reverse transcriptase inhibitor, one non-nucleoside reverse transcriptase inhibitor, and one or two protease inhibitors for three to six months or documented resistance to members of each antiretroviral class, and (2) persistent viremia (HIV RNA > 5,000 copies/ml). Subjects were randomized 2:1 to enfuvirtide plus a newly selected 'optimized background'(OB) regimen (based on phenotype and genotype assays), or to an optimized background regimen alone. Subjects were stratified by both number of newly approved or investigational drugs in the OB regimen (0, 1, or 2) and by HIV RNA level at screening (<40,000 or ≥40,000 copies/ml) prior to randomization.

Six hundred seventy-three subjects in both studies were randomized to enfuvirtide + OB and 340 to OB alone. Most had advanced HIV disease as evidenced by low CD4 cell counts at entry (mean = 92 cells/mm^3). Subjects had previously received a mean of 12 antiretroviral drugs and had been on antiretroviral drugs for a mean of seven years prior to study entry. Resistance to currently available antiretroviral drugs was common in both treatment groups.

Enfuvirtide was self-administered by subcutaneous injection at a dose of 90 mg twice daily. Both enfuvirtide + OB and the OB alone regimens were started on study day one. Subjects in the OB arm who experienced virologic failure could switch to an enfuvirtide containing regimen any time after week 8. Subjects in the enfuvirtide arm who experienced virologic failure could choose to remain on enfuvirtide and stay on study.

The primary efficacy endpoint was the change in plasma HIV RNA levels from baseline to week 24. Secondary efficacy endpoints included virologic response, change in CD4 count, AIDS defining events, and death.

The change in plasma HIV-1 RNA from baseline to week 24 was -1.55 log$_{10}$ copies/ml for subjects receiving enfuvirtide + OB compared to -0.71 for subjects in the OB arm. Subjects in the enfuvirtide + OB arm had a greater decrease in viral load (−0.846 log$_{10}$ copies/ml, p<0.001). Treatment benefit with enfuvirtide was also demonstrated within each treatment stratum.

In the three predefined categories of virologic response (HIV RNA <50 copies/ml, HIV RNA <400 copies/ml, and ≥ 1.0 log$_{10}$ copies/ml decrease in HIV RNA from baseline), the proportion of subjects in the enfuvirtide + OB arm achieving a virologic response at week 24 was greater than in the OB alone arm (p<0.001). By week 24, 45.5% of subjects in the enfuvirtide + OB arm and 71% in the OB arm had experienced virologic failure. The mean change in CD4 count from baseline to week 24 for subjects in the enfuvirtide + OB arm was +71 cells/mm^3 and for subjects in the OB alone arm was +35

cells/mm^3. There was no statistical difference between the two treatment groups in AIDS defining illnesses or death at 24 weeks.

Efficacy data from the analysis of both Phase 3 studies of enfuvirtide demonstrated a significant effect of an antiretroviral regimen containing enfuvirtide compared to a regimen without enfuvirtide. This is considered unequivocal evidence of antiviral activity in an experimental design that has been recommended to sponsors by FDA. The magnitude of the effect seen is believed to be clinically meaningful based on analyses of earlier studies correlating virological and immunological changes with clinical efficacy.

C.   Safety

A total of 1541 subjects were reported as having received at least one dose of enfuvirtide in clinical trials. Of these, 1401 have received enfuvirtide at the dose proposed for labeling (90 mg BID in adults and 2.0 mg/kg for children ages 6 years and older). A total of 913 subjects have received enfuvirtide for at least 24 weeks, and 569 subjects for at least 48 weeks. All subjects received adequate monitoring and follow-up for determination of safety.

Since adverse events are common in HIV-infected persons receiving antiretroviral therapy, the safety of enfuvirtide was assessed by comparing the two arms in the Phase 3 clinical trials where subjects were randomized to either enfuvirtide plus an optimized antiretroviral background regimen or to an optimized background regimen alone. In the Phase 3 studies, 673 subjects were randomized to enfuvirtide + OB and 340 to OB alone. Subjects in the OB arm with virologic failure could switch to an enfuvirtide containing regimen any time after week 8 while subjects in the enfuvirtide + OB arm with virologic failure could choose to remain on enfuvirtide. Therefore, exposure to study drug was greater in the enfuvirtide + OB arm and increased over time as subjects left the OB alone arm; by week 24 the exposure on originally randomized therapy arm was 2.9 fold greater in the enfuvirtide + OB arm. Since the incidence of adverse events was not always corrected for exposure by the sponsor, differences in exposure must be taken into account when reviewing the proportion of subjects with any particular adverse event.

Local injection site reactions (ISRs) were by far the most common adverse event reported in subjects receiving enfuvirtide and were reported in almost all subjects: 98% in Phase 3 studies. The majority of subjects reported an ISR at the first study visit (86%), and continued to report ISRs throughout the study. Most ISRs (95%) were associated with pain or discomfort: 9% of subjects required analgesics or narcotic analgesics for the pain associated with an ISR. Individual signs and symptoms were commonly reported, particularly erythema (89%), induration (89%), and nodules or cysts (76%). The erythema was often extensive and more than 30% of subjects had erythema > 50 mm in diameter. Almost one-half of subjects had Grade 3 or 4 induration ($\geq$ 25 mm). Approximately 25% of subjects had nodules or cysts that were $\geq$ 30 mm.

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Most subjects had one to five lesions at any one time; individual lesions usually lasted less than 7 days. The severity and frequency of ISRs did not appear to increase over time. Despite the high frequency of ISRs, only 4% of subjects discontinued the study because of ISRs. Infectious complications of ISRs, such as cellulitis and abscess formation, occurred in approximately 1% of subjects. One subject required hospitalization for an injection site abscess.

The morbidity and frequency of this adverse effect mandates that healthcare providers prescribing enfuvirtide and patients initiating enfuvirtide be educated regarding the signs and symptoms of ISRs. ISRs are certain to occur in almost every patient who receives enfuvirtide and will be an important reason that patients discontinue treatment with enfuvirtide. Healthcare providers must learn to distinguish typical signs and symptoms of ISRs from infection at the injection site, and patients must be educated regarding signs and symptoms that warrant seeking medical attention. As enfuvirtide is used in larger and more heterogeneous populations than previously studied (and under less controlled conditions than in clinical trials), infectious complications are likely to be seen in a greater proportion of patients. There is no known pretreatment to minimize the symptoms of ISRs, but a pilot study examining several interventions is ongoing. As validated methods to decrease the signs and symptoms of ISRs evolve, the sponsor must revise all educational materials and disseminate this information as soon as it becomes available.

Despite the frequency of ISRs and associated morbidity, permanent sequelae or long-term complications from ISRs did not occur in either Phase 3 study. Although ISRs may deter initiation of enfuvirtide by some individuals (and lead to discontinuing use in others), overall it is believed that this is a manageable risk. The other events most frequently reported in subjects receiving enfuvirtide + OB in Phase 3 studies, were diarrhea (26.8%), nausea (20.1%), and fatigue (16.1%). These rates were comparable to those observed in the background regimen alone. A higher proportion of subjects receiving enfuvirtide + OB had pancreatitis, peripheral neuropathy, depression, and anxiety, although the absolute incidence of each was low.

Serious hypersensitivity reactions were seen in 5 subjects receiving enfuvirtide (<1%), with recurrence on rechallenge in 3. Five of these episodes were judged to be related to enfuvirtide including one subject with rash, fever, and vomiting; one with rash, nausea, chills, and hypotension; one with fever, maculopapular rash, and increased transaminases; one with primary immune complex reaction; and one with membranoproliferative glomerulonephritis. Three episodes of hypersensitivity recurred on rechallenge with enfuvirtide; the symptoms on rechallenge included rash, fever, rigors, vomiting, hypotension, and worsening ISR. Although hypersensitivity reactions associated with enfuvirtide are uncommon, healthcare providers and patients must be aware of the signs and symptoms of hypersensitivity reactions because of their potential severity and the possibility that they may recur on rechallenge. Both the package insert and patient package insert for enfuvirtide caution patients regarding possible hypersensitivity reactions.

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Bacterial pneumonia was observed more frequently in the Phase 3 studies in subjects randomized to enfuvirtide + OB arm versus the OB arm (4.68 events/100 patient years compared to 0.61 events/100 patient years).The incidence of developing pneumonia in the enfuvirtide arm did not increase over time on study. Slightly more than half of the subjects with pneumonia required hospitalization. Three subjects with pneumonia died; all three had profound immunosuppression (CD4 count < 50 cells/mm^3) and coexisting illness (lymphoma, sarcoma, and CNS disease). Development of pneumonia was more common in subjects with low CD4 counts, in current or past smokers, in subjects with a history of lung disease, and in subjects with a history of intravenous drug use. Despite this finding of a difference between the study arms, it is unclear if the development of pneumonia was related to enfuvirtide use. There was no other evidence of immunosuppression: the incidence of neutropenia and lymphopenia were higher in the OB arm than the enfuvirtide + OB arm, CD4 counts increased in the enfuvirtide + OB subjects, and there was no predilection for any particular microorganism or pattern of illness consistent with any known immune abnormality. It is possible that the higher incidence of pneumonia in enfuvirtide recipients was related to study design: subjects in the OB group could discontinue the study after virologic failure, so the subjects remaining on study in the OB group were 'limited' to subjects experiencing virologic and immunologic improvement on their study drugs. Finally, the incidence of pneumonia observed in subjects receiving enfuvirtide was consistent with the incidence of pneumonia in HIV-infected subjects reported in the scientific literature while the incidence of pneumonia in the OB arm was abnormally low. However, since an immunosuppressive effect of enfuvirtide cannot be excluded (especially as the first member of a new drug class), information about this finding must be included in the Warnings section of the Package Insert and in the all patient/practitioner educational material. Risk factors for the development of pneumonia should also be included in package labeling.

Results from in vitro and in vivo studies suggest that enfuvirtide is unlikely to have significant drug interactions with concomitantly administered drugs metabolized by CYP450 enzymes.

All clinical studies of enfuvirtide enrolled treatment experienced subjects, and many of the subjects in the Phase 3 clinical studies had advanced HIV disease. HIV-infected patients receiving enfuvirtide after marketing are similarly likely to have advanced HIV disease. The types of adverse events should not be different in patients who receive enfuvirtide commercially, but the incidence of adverse events post approval may be greater due to less controlled clinical settings and more heterogeneous patient populations. Another concern is the duration of drug effect. Although at the time of NDA filing more than 500 subjects received enfuvirtide for more than 48 weeks, patients receiving enfuvirtide post approval may require drug indefinitely. Over time, the increasing emergence of resistance is likely to reduce clinical effectiveness as treatment time becomes extended. At this time there is no standardized commercial assay for

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enfuvirtide resistance, nor any information whether a favorable effect on virulence supports dosing even in the presence of *in vitro* resistance.

Both hypersensitivity reactions and pneumonia must be cited as Warnings in the package insert since each represents a potentially fatal adverse event. Injection site reactions occur in the majority of subjects receiving enfuvirtide and are associated with considerable morbidity; therefore, ISRs should also be included in the Warnings section.

D.   Dosing

Enfuvirtide was administered as a regimen of 90 mg injected subcutaneously twice daily in the Phase 3 studies. Dose selection was based on the results of three studies. In two dose finding studies, the 90 mg dose was associated with the greatest decrease in plasma HIV RNA levels at 15 days or at 28 days. The third study was not interpretable due to a high dropout rate. Although based on limited information the 90 mg twice daily appears to be an appropriate choice. There is the suggestion that higher doses may be more active but are impractical for administration.

There are no data to support a relationship between any pharmacokinetic parameter of enfuvirtide with either a safety or efficacy endpoint.

In Phase 3 studies of enfuvirtide, enfuvirtide was temporarily or permanently discontinued after recurrent Grade 3 or Grade 4 adverse events. There is no evidence to support use of a dose lower than 90 mg twice daily. Therefore, dose modifications are not recommended for enfuvirtide .

E.   Special Populations

Enfuvirtide was studied in two Phase 3 clinical trials conducted in 1013 treatment experienced HIV-infected subjects. The majority of subjects in these trials were white (89%) and male (90%). The mean age of subjects in these two studies was 42 years.

Gender: The treatment effect of enfuvirtide was greater than that of the active control in all subgroups analyzed, including females and non-whites. The treatment effect was statistically significant for non-whites. Although females in the enfuvirtide + OB group had a greater decrease in viral load from baseline to week 24 than the control OB arm (−1.617 versus −1.045 $\log_{10}$ copies/ml), the difference was not statistically significant. The lack of statistical significance may relate to the small number (n=102) of females enrolled in these trials. In addition, a −1.045 $\log_{10}$ decrease in viral load was observed in females in the OB arm, compared to a −0.745 $\log_{10}$ decrease in males; while the treatment response in females and males in the enfuvirtide + OB groups was similar, -

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1.617 and 1.574 $\log_{10}$ respectively. The reason for the greater treatment response in females on the OB arm is unclear. Finally, the absolute effect size of the enfuvirtide + OB arm (-0.572 $\log_{10}$) was similar to that seen in other subgroups. In summary, a treatment effect was observed for females receiving enfuvirtide + OB compared to OB alone in Phase 3 studies; however, this effect was not statistically significant likely due to of the small number of females enrolled in the study and the greater treatment response to OB alone in females.

Analysis of plasma concentration data from subjects in clinical trials of enfuvirtide indicates that the clearance of enfuvirtide is 20% lower in females than males after adjusting for body weight. This difference in clearance did not appear to affect the activity of enfuvirtide in females. Overall, there did not appear to be a difference in safety by gender, but the strength of this conclusion is limited by the relatively small number of women enrolled.

Ethnicity: Analysis of plasma concentration data from subjects in clinical trials indicated that the clearance of enfuvirtide was not different in black subjects compared to white subjects. Other pharmacokinetic studies suggest no difference between subjects of Asian heritage and white subjects after adjusting for body weight. There was an insufficient number of non-white subjects to analyze data for the treatment effect in specific ethnic minorities; however, there was a statistically significant treatment benefit for all non-white subjects receiving enfuvirtide + OB collectively compared to OB alone, similar to the effect seen in white subjects.

Age: The mean age of subjects in the Phase 3 clinical studies was 42 years. Only two enfuvirtide recipients in these studies were older than 65 years of age. The pharmacokinetics of enfuvirtide have not been studied in patients over 65 years of age.

Hepatic/Renal dysfunction: Formal pharmacokinetic studies of enfuvirtide have not been conducted in patients with hepatic impairment or in patients with renal insufficiency. Analysis of plasma concentration data from subjects in clinical trials indicated that the clearance of enfuvirtide is not affected by renal function in patients with creatinine clearance greater than 35 ml/min. The effect of creatinine clearance less than 35 mL/min on enfuvirtide clearance is unknown. Additional data on the pharmacokinetics of enfuvirtide in patients with renal insufficiency has been requested in post-approval studies. However, as a peptide, it is not anticipated that either renal or hepatic disease will affect the clearance of enfuvirtide.

Pregnancy: Reproduction studies conducted in rats and rabbits revealed no harm to the fetus from enfuvirtide at doses up to 27 and 3.2 times the adult human dose on a m^2 basis, respectively. There are no adequate and well-controlled studies in pregnant women. Enfuvirtide will be labeled as Pregnancy Category B. The applicant has arranged that pregnancy outcomes in women who are exposed to enfuvirtide during pregnancy can be monitored in the Antiretroviral Pregnancy Registry.

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Children: Enfuvirtide was studied in two single arm, open-label, pharmacokinetic, safety and efficacy studies in 39 children three years of age and older. In one of these studies, 10 of the 11 study subjects completed 48 weeks of treatment with a combination of enfuvirtide and other antiretroviral drugs. By week 48, 6/11 (55%) subjects had ≥ 1 log_{10} decline in HIV-1 RNA, and 4/11 (36%) subjects were below 400 copies/mL of HIV-1 RNA. The median changes from baseline in HIV-1 RNA and CD_4 cell count were -1.48 log_{10} copies/mL and 122 cells/μL, respectively. The overall adverse event profile of enfuvirtide was similar in pediatric patients to that in adults; as in adults, injection site reactions were the most common adverse event. The other pediatric study is ongoing. There were too few pediatric patients from 3 to 5 years of age (n=5) enrolled in these studies to determine either the pharmacokinetics or the safety of enfuvirtide in this age range. Therefore, enfuvirtide at a dose of 2 mg/kg twice daily should be approved for use only in children 6 years of age and older. The pharmacokinetics and safety of enfuvirtide in pediatric patients from 3 to 5 years of age are currently being studied, and the applicant has committed to submission of this data as a Phase 4 commitment. FDA has discussed the pediatric development plan for enfuvirtide with the applicant; additional studies in children younger than 3 years of age are expected in the future.

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Clinical Review

I. **Introduction and Background**

A. **Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups**

Established name: Enfuvirtide (T-20)
Trade Name: Fuzeon™
Chemical: $C_{204}H_{301}N_{51}O_{64}$
Class: Fusion inhibitor
Proposed indication: Treatment of HIV-1 infection in treatment-experienced patients with evidence of HIV-1 replication despite ongoing antiretroviral therapy
Dose and regimen: adults: 90 mg twice daily by subcutaneous injection
pediatric patients: 2 mg/kg twice daily by subcutaneous injection
Dosage form: vial containing 108 mg of enfuvirtide for the delivery of approximately 90 mg/1 mL when reconstituted with 1.1 ml of Sterile Water for Injection

Fuzeon (enfuvirtide, T-20) is the first entry inhibitor to be reviewed for approval in the United States. Enfuvirtide acts at the first stage of HIV infection of new cells by preventing the fusion of HIV to CD4 positive cells.

Enfuvirtide in combination with other antiretroviral drugs is indicated for the treatment of HIV-1 infection in treatment experienced patients. Most study subjects in the Phase 3 trials of enfuvirtide had advanced HIV disease; enfuvirtide has not been studied in treatment naïve patients. T20 is a 36 amino acid peptide and must be administered twice daily by subcutaneous injection. The dose for adults is 90 mg twice daily and for children six years of age and older is 2 mg/kg twice daily.

B. **State of Armamentarium for Indication(s)**

FDA has approved 17 antiretroviral drugs in three classes for the treatment of HIV in adults: nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, and protease inhibitors. The use of antiretroviral drugs in combination has decreased the morbidity and mortality of HIV disease. However, treatment with combination therapy is often associated with significant drug toxicities such as fat redistribution, hyperglycemia, pancreatitis, and lactic acidosis. In addition, resistance to antiretroviral drugs often develops during treatment and resistance to one antiretroviral drug in a class often confers resistance to the entire class. Resistance to existing

antiretroviral therapy is widespread. There is an urgent need for new drugs from new antiretroviral classes, particularly drugs with unique resistance patterns.

Enfuvirtide is the first entry inhibitor to be reviewed for marketing in the United States. It prevents fusion of HIV-1 to the CD4 cell membrane. Currently available antiretroviral drugs block steps of HIV replication after HIV enters the cell. Since enfuvirtide is the first fusion inhibitor, the patterns of mutations conferring resistance are unique, and enfuvirtide will offer a treatment option for patients with multidrug resistant HIV.

Enfuvirtide will be the only currently available antiretroviral drug specifically indicated for treatment of HIV in treatment experienced patients. All Phase 3 trials of enfuvirtide were in treatment experienced subjects. Although enfuvirtide is administered parenterally and its use is associated with significant injection site reactions, in most cases the ISRs were tolerable, and the overall toxicity profile in the context of the patients to be treated favor its use. Therefore, risk/benefit assessment supports enfuvirtide use in treatment experienced patients.

C. Important Milestones in Product Development

The original Investigational New Drug Application for enfuvirtide was submitted on October 14, 1996. The first clinical trial in humans began in November 1996. A clinical development meeting was held with the sponsor on March 10, 2000 to discuss study designs for Phase 3 trials. An End of Phase 2 meeting was held on September 29, 2000. Additional clinical and chemistry meetings were held on June 11, 2002 to discuss the New Drug Application and manufacturing issues. In addition, clinical development issues regarding enfuvirtide, including trial design, study conduct, and statistical analyses, were discussed in numerous teleconferences with the applicant.

D. Other Relevant Information

Enfuvirtide is not marketed in any country.

E. Important Issues with Pharmacologically Related Agents

Enfuvirtide is the first fusion inhibitor to be submitted for approval in the United States. Another fusion inhibitor, T-1249, is in Phase 1 development. It is significant that preliminary data in studies of T-1249, shows *in vivo* activity in patients previously exposed to enfuvirtide (as reported recently at the 10th Conference on Retroviruses and Opportunistic Infections).

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II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

A. Chemistry:

For a detailed discussion of Chemistry, Manufacturing and Controls, please see Dr. Rao Kambhampati's review.

The drug product is manufactured by F. Hoffmann-La Roche Ltd., Basel (Switzerland) and ——————————————————— The drug substance is manufactured, packaged, tested, and released at the facilities of Roche in Boulder, CO. Enfuvirtide is a chiral, 36-amino acid synthetic polypeptide with the N-terminus acetylated. It is composed of naturally occurring L-amino acid residues. The enfuvirtide drug substance is manufactured by ——————— approach, in which '——— fragments, —————————————————————————— are produced by ———

Satisfactory batch analysis data were provided for—NDA registration batches, ~ recent Phase— clinical batches, and— commercial size batches (which included— validation batches). The stability data included 12 months long-term (5°C) and 6 months accelerated (25°C/60%RH) data for— registration batches that were made at :——————— using the commercial process.

Fuzeon™, is a sterile lyophilized powder for subcutaneous injection. The powder is packaged in single-dose glass vials. Each vial contains 108 mg of enfuvirtide drug substance (for the delivery of 90 mg) as the active ingredient and the following excipients: mannitol ———— ,. sodium carbonate anhydrous ———— sodium hydroxide ———— , and hydrochloric acid ———— Prior to subcutaneous administration, the contents of the vial are reconstituted with 1.1 mL of Sterile Water for Injection, giving a volume of approximately 1.2 mL to provide the delivery of 1 mL of the solution containing 90 mg of enfuvirtide.

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The manufacturing process consists of ⸺⸺⸺⸺⸺⸺⸺⸺⸺⸺⸺ and ⸺⸺⸺ :. The process flow diagrams, manufacturing descriptions, in-process controls, and executed batch record were provided in the NDA submission. Sterilization process documentation for an ⸺⸺⸺ product for both sites was provided. The primary container/closure system consists of⸺⸺⸺⸺⸺ glass vial, ⸺⸺⸺ ⸺⸺⸺⸺⸺ stopper with a ⸺⸺⸺⸺ and . ⸺⸺⸺⸺⸺ The specification for the drug product included container (size and appearance), content of container (appearance and color), reconstituted solution (appearance, reconstitution time, degree of coloration, pH, particulate matter), water content, uniformity of mass/uniformity of dosage units (wt. variation), identity for Ro 29-9800 (enfuvirtide) by ⸺⸺ and ⸺ or ⸺⸺⸺ content per vial of Ro 29-9800 by ⸺⸺ . degradation products by ⸺⸺ . sterility, and bacterial endotoxins. Batch analysis was provided for ⸺⸺ batches each made at Roche (Basel) and ⸺⸺⸺⸺The stability data included 15 months long-term (25°C) and 6 months accelerated (40°C) data, and statistical analysis of the data for ⸺⸺ registration batches that were made at Roche, Basel. 3 months long term and accelerated data were provided for ⸺⸺ batch that was made at ⸺⸺⸺. In addition, supportive stability data (up to 24 months long-term) were provided for ⸺⸺ clinical batches that were made at ⸺⸺⸺⸺⸺. The reconstituted Fuzeon vials were demonstrated to be physically and chemically stable for up to 48 hrs at 2-8°C and for 24 hrs at room temperature.

B. Animal Pharmacology and Toxicology:

For a detailed discussion of the Pharmacology and Toxicology program, please see Dr. William Taylor's review.

The principal nonclinical findings were injection site reactions and antibody production. Injection site reactions were observed in rats, guinea pigs, minipigs, and cynomolgus monkeys. The injection site reactions ranged from minor tissue discoloration to granulomatous inflammation, hemorrhage, fibrosis, edema and necrosis (including both dermal and muscle tissues). In addition, microscopic changes in the spleen and thymus that are consistent with injection site hypersensitivity reactions were observed in the monkey.

Changes in hematology and clinical chemistry parameters that are consistent with injection site reactions were observed in the rat and monkey. In a 9-month toxicity study in the monkey, enfuvirtide administration was associated with elevated numbers of eosinophils in most (≥70%) treated animals compared with controls. One of four animals held over to 10 months (recovery period) had an elevated eosinophil count at necropsy (approximately twice the eosinophil count as the control). Effects were higher in males than in females but were not dose-related.

Antibody titers to enfuvirtide were measured in the rat, minipig, and monkey. Skin sensitization (delayed contact hypersensitivity) from intradermal injections and direct skin application of enfuvirtide was demonstrated in the guinea pig.

C. Microbiology:

For a detailed discussion of the clinical virology program, please see Dr. Nara Battula's review.

Mechanism of action: Enfuvirtide is a 36 amino acid synthetic peptide composed of L-amino acids. The primary amino acid sequence was derived from a naturally occurring motif, the heptad repeat 2 region, which is located within the HIV-1 envelope glycoprotein gp41. Normally, the HIV envelope protein, gp120, binds to a cell using the CD4 receptor and a co-receptor; this triggers the formation of a gp41 coil in which gp41 domain folds back on itself so that the N-terminus of gp41 can insert into the cellular membrane of the host. Enfuvirtide binds to gp41 so that gp41 cannot form a coil preventing the fusion of HIV to the cell membrane.

HIV Resistance to enfuvirtide: Enfuvirtide was active against HIV-1 isolates with resistance to nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, and protease inhibitors. This was evaluated in the study of 86 recombinant virus constructs and 35 primary clinical isolates containing resistance mutations to reverse transcriptase and protease. The sensitivity of virus isolates was independent of their resistance to any of the currently approved antiretroviral classes.

Specific mutations that result in reduced susceptibility to enfuvirtide were demonstrated through *in vitro* selection and site-directed mutagenesis and by the sequencing of clinical isolates from patients experiencing virologic failure on enfuvirtide. Emergence of resistance was studied *in vitro* using cell cultures infected with HIV that were sequentially passaged in increasing concentrations of enfuvirtide. After five passages of the virus over a five to six week period, enfuvirtide resistant virus emerged. The envelope region of the resistant virus was amplified and sequenced to determine the genetic basis of enfuvirtide resistance, and changes were observed in amino acids 36 to 38 of the gp41 gene. These results were confirmed by studies of site-directed mutagenesis in which mutations were introduced at amino acids 36 to 38. Reduced susceptibility to enfuvirtide, including mutations resulting in more than 10 fold resistance, was observed with single mutations.

Enfuvirtide resistance in viral isolates from subjects enrolled in clinical trials has also been observed. Susceptibility to enfuvirtide was evaluated on viral isolates from subjects receiving enfuvirtide in Phase 3 clinical trials at baseline, week 24, week 48, and at virologic failure. See the Appendix for a detailed description of these studies. Genotypic changes in clinical isolates covered a wider region and were reported in amino acids 36 to 45 of gp41. Decreased susceptibility was seen with both single and double mutations. The most common amino acid substitution, V38A, was observed in 9% of isolates of subjects experiencing virologic failure. The second most common substitution, N43D, was noted in 19 isolates (6.3%). Phenotypic resistance data was available for 206 subjects receiving enfuvirtide who experienced virologic failure in a

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Phase 3 clinical trials. Viral envelopes from 91% of subjects with virologic failure had a greater than four-fold change in EC_{50} from baseline to virologic failure. The geometric mean change was 21 fold (range of <1 to 422 fold). Susceptibility varied by amino acid substitution and was highest for the most common substitution (41.6 fold decreased susceptibility with V38A). The N43D substitution resulted in a mean change of 26.4 fold.

In summary, genotypic and phenotypic resistance was observed both *in vitro* and in clinical samples of subjects receiving enfuvirtide in clinical studies. Single amino acid mutations resulted in substantial reductions in susceptibility. Enfuvirtide is indicated for treatment experienced patients: if enfuvirtide is added to an already ineffective antiretroviral regimen, enfuvirtide will be acting as functional monotherapy and resistance will develop fairly quickly. In order to prevent a relatively short lived clinical response, it is important that patients receive other active agents in their regimen.

Antibodies to gp41: Since patients produce antibody to gp41 and this antibody could potentially crossreact with enfuvirtide, all subjects in studies T20-301 and T20-302 had baseline, week 8, and week 24 measurements of gp41 antibody. At baseline, 77% (477/616) of subjects in the enfuvirtide + OB arm and 74% (221/298) in the OB alone arm were positive for gp41 antibody. At week 24, 68% of subjects in the enfuvirtide + OB arm and 79% in the OB alone arm had detectable levels of antibody to gp41.

Although changes in antibody level over time were observed, most subjects had measurable antibody at baseline and at week 24. Seventy-eight percent of subjects with measurable antibody at baseline also had measurable antibody at week 24. Only four subjects in the enfuvirtide + OB group had positive antibody titers at baseline and negative levels at week 24. In the OB group, no subjects went from a positive to a negative antibody titer. Among subjects in the enfuvirtide + OB group who were antibody positive at both timepoints, 65% had a 30% or greater decrease in gp41 antibody from baseline to week 24; 8% had a 30% or greater increase in antibody, and 27% had changes within 30% of baseline. Decreases in gp41 antibody levels from baseline were less common in the OB group (13%); the majority of subjects (76%) in the OB group had week 24 antibody levels within 30% of baseline. Of the six subjects in the enfuvirtide + OB group with negative titers at baseline, two remained negative at week 24, three were not quantifiable, and one was positive. Only one subject in the OB group had a negative titer at baseline; his titer at week 24 was not quantifiable. Although multiple patterns of change over time in antibody levels were observed, overall there was a mean decrease in gp41 antibody titer at week 24 in both treatment groups.

When analyzed by change in gp41 antibody, no relationship between gp41 antibody level and change in viral load was observed. Specifically, an increase in antibody to gp41 did not predispose subjects on enfuvirtide to virologic failure; in contrast, a greater proportion of subjects in the enfuvirtide + OB group had decreases in gp41 antibody from baseline to week 24. Since so few subjects were antibody negative at baseline, efficacy results could not be analyzed for this group. In the safety analysis, no specific

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adverse event or pattern of adverse events correlated with specific changes in gp41 antibody level. In particular, increases in gp41 antibody levels did not appear to be associated with hypersensitivity reactions or injection site reactions.

In summary, neither the presence of antibodies to gp41 or the change in gp41 antibody level over time appeared to influence the efficacy or safety of enfuvirtide.

Viral coreceptor tropism: The applicant analyzed HIV envelope coreceptor tropism in viral isolates from baseline and at the time of virologic failure in subjects receiving enfuvirtide in Phase 3 studies. The majority of subject isolates (378 or 62%) were R5 single tropic at baseline but 211 (34.5%) were dual tropic and 23 (4%) were R4 tropic. For the majority of paired isolates, envelope coreceptor tropism was identical at baseline and at the time of virologic failure. Viral envelope from 13 subjects (10%) changed tropism from R5 to X4 at virologic failure; envelope from two of six subjects changed from X4 to R5. Viral isolates from 27 (56%) with dual tropism at baseline had single tropism at the time of virologic failure (3 with X4 and 24 with R5). Although it is of concern that virologic failure after treatment with enfuvirtide could be associated with a change in viral tropism in a small proportion of subjects, definitive conclusions cannot be reached from this data because the results from the control group (subjects in the optimized background arm experiencing virologic failure) were not provided by the applicant.

D. Statistics:

For a detailed discussion of the statistical analysis of efficacy, please see Dr. Tom Hammerstrom's review.

In two Phase 3 trials, studies T20-301 and T20-302, subjects were randomly assigned in a 2:1 ratio to receive either enfuvirtide plus an optimized background regimen or the optimized background regimen alone. No blinding or placebo was used since enfuvirtide is administered by subcutaneous injection, and injection site reactions are extremely common. The primary efficacy endpoint was the change in plasma HIV-1 RNA from baseline to week 24.

Enfuvirtide + OB was statistically significantly superior to OB alone in both Phase 3 trials with respect to the primary endpoint specified in the protocol. The findings were robust to handling of missing data, to sensitivity analyses, and to analyses of subpopulations.

Please see the following section for a discussion of the Clinical Pharmacokinetics findings.

III. Human Pharmacokinetics and Pharmacodynamics

A. Pharmacokinetics

For a detailed discussion, please see Dr. Robert Kumi's's Clinical Pharmacology review.

Two Phase 3 clinical trials and 14 pharmacokinetic (PK) studies were conducted in support of the enfuvirtide application. In addition, a population PK analysis and *in vitro* studies were included in the NDA submission. At the proposed dose (90 mg twice daily), the mean PK measures for enfuvirtide in adults are: AUC $\approx$ 44 μg·hr/mL, $C_{max} \approx$ 5 μg/mL, $C_{min} \approx$ 3 μg/mL, and median $T_{max} \approx$ 4 hr.

Absorption: Approximately 80 % of enfuvirtide is absorbed following subcutaneous (SC) administration of enfuvirtide (45 to 180 mg single dose). Maximal enfuvirtide concentrations were obtained between 5 and 7 hours post dose, followed by a monoexponential decline in drug concentrations. Enfuvirtide appears to exhibit flip-flop kinetics ($t_{1/2}$ IV < apparent $t_{1/2}$ SC). Absorption was independent of SC administration site (arm, thigh and abdomen).

Dose proportionality: Exposure of enfuvirtide increased in an approximately dose proportional manner following single dose administration over the 45 to 180 mg dose range. The data provided were insufficient to make a definitive conclusion regarding dose-proportionality following multiple dose administration.

Accumulation: Following multiple dose administration at the proposed clinical dose, approximately 30% accumulation occurs.

Distribution: Enfuvirtide is greater than 90% bound to plasma proteins, particularly albumin. The volume of distribution was approximately 5 L following a 90 mg intravenous dose of enfuvirtide.

Demographic Characteristics (Race, Gender and Body Weight): The clearance of enfuvirtide is affected by gender and body weight; enfuvirtide clearance is not affected by race. The enfuvirtide clearance in female subjects is 20 % lower than in male subjects having the same body weight. Enfuvirtide clearance decreases with decreased body weight, irrespective of gender.

Metabolism: Enfuvirtide is expected to undergo catabolism rather than metabolism. *In vitro* studies (microsomes and hepatocytes) indicate that enfuvirtide is broken down into ———— degradation products (———————). Only the deamidated metabolite, ——; or Ro 50-6343, has been characterized in clinical pharmacology studies.———accounts for less than ——; of total enfuvirtide exposure.

Elimination: Enfuvirtide has a low systemic clearance (after IV administration) of approximately 1.5 L/h, and has a short elimination half-life, $t_{1/2}$ < 4 hr.

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Drug-drug interactions: Based on *in vitro* and *in vivo* metabolism data, enfuvirtide has a low potential to undergo cytochrome P-450 (CYP) based drug-drug interactions at clinically relevant concentrations. *In vitro* studies indicate that enfuvirtide does not inhibit the major CYP enzymes. *In vivo* studies suggest that enfuvirtide does not alter the pharmacokinetics of common CYP substrates. However, enfuvirtide exposure was increased ⸺⸺ in the presence of ritonavir; the mechanism of the interaction is not known. The influence of transporters on enfuvirtide pharmacokinetics has not been characterized.

Pediatric subjects: Pediatric subjects between 5 and 17 years old receiving 2.0 mg/kg enfuvirtide achieve enfuvirtide exposure that is comparable to that in adults receiving the 90 mg dose; however, data in pediatric subjects are more variable than in adult subjects. Data provided are insufficient to make dosing recommendations for children < 6 years old. (See Dr. Kassa Ayalew's review for more information.)

B. Pharmacodynamics

In early trials of enfuvirtide, the dose was estimated on the fill volume of the drug vial. Studies of the delivered dose, showed that doses of 50 mg actually delivered 48.7 mg while doses of 100 mg delivered 90 mg, the approved dose of enfuvirtide. The doses reported in this review refer to the doses named in the study protocol and not necessarily the delivered dose of drug.

1. Dose-Response Relationship

Enfuvirtide exposure-response relationships have not been well studied. In early clinical trials, there was some indication that a dose-response relationship exists. The 90 mg SC dose was the most active of all subcutaneous doses evaluated (the range of doses studied was 45 to 90 mg), and was as safe as all other tested doses; thus this dose was chosen for the pivotal clinical studies. In study TRI-001 the applicant targeted a trough level of 1 µg/ml, because of *in vitro* study results demonstrating an IC_{50} for HIV suppression of 1 µg/ml. However, no clear exposure-response existed for the C_{trough} exposure measure and antiretroviral efficacy.

Study ⸺-001
Study⸺-001 was a Phase I/2 study of the safety, pharmacokinetics, and antiretroviral activity of intravenous enfuvirtide in 17 HIV-infected adults. Enrolled subjects could be treatment experienced and treatment naïve with a CD4 count of 100 cells/mm^3 or greater and a plasma HIV RNA level of 10,000 copies or greater. Subjects could not have received other antiretroviral drugs within 15 days of study entry. Study subjects were sequentially assigned to one of four enfuvirtide dose groups: 3, 10, 30, and 100 mg administered intravenously twice daily. Enrollment began at the lowest dose group

and progressed to successively higher dose groups. Subjects received a single intravenous dose on day one and the identical dose twice daily for 14 days beginning on study day 4.

The primary study objectives were to assess safety and pharmacokinetics of both single and multiple doses of intravenous enfuvirtide administered. Safety information was collected at each study visit. Enfuvirtide pharmacokinetic measurements were obtained on days 1 and 7. Because the IC_{50} in peripheral blood mononuclear cells was 1 µg/ml, the study attempted to determine if any of the enfuvirtide doses resulted in trough concentrations greater than 1 µg/ml. The secondary objective of this study was to assess antiviral activity as measured by changes in CD4 count and plasma HIV-1 RNA levels after 14 days of enfuvirtide. Plasma HIV RNA levels were obtained at screening, at baseline, on days 4, 7, 11, 14, 17, and at follow-up.

Seventeen subjects enrolled in study——001. Study subjects were predominantly male (94%); nine (53%) were Caucasian and eight (47%) were Black. Mean age for subjects in each treatment group ranged from 33 to 36 years. The median baseline plasma HIV RNA level was similar in the four treatment groups and ranged from 4.2 to 5.1 $\log_{10}$ copies/ml. The mean CD4 count at baseline ranged from 248.8 to 486.0 cells/mm^3. Previous exposure to antiretroviral drugs varied between treatment groups. All four subjects in the 100 mg BID group were treatment naïve, while all subjects in the other treatment groups were treatment experienced.

One subject withdrew consent and discontinued the study prematurely after receiving two doses of study drug.

Pharmacokinetic parameters were measured during the 24 hours following the initial dose of enfuvirtide and for 12 hours following the morning dose on study day 7. Exposure, peak concentration, and trough levels were dose dependent. The 100 mg BID dose was the only dose to achieve trough concentrations greater than 1.0 µg/ml.

Changes in plasma HIV RNA from baseline to day 18 is shown in Table 1 below.

Table 1: Change in Plasma HIV RNA from Baseline to Day 18 in Study TRI-001

	3 mg BID	10 mg BID	30 mg BID	100 mg BID
Mean Change	-0.1±0.05	-0.1±0.10	-0.5±0.25	-1.5±0.10
% of subjects with ≥1 log ↓ in RNA	0	0	25%	100%

Source: CSR submitted July 16, 2002, Volume 132, page 60.

The change in plasma HIV RNA was dose related. Reductions in plasma HIV-RNA levels were noted in subjects receiving 30 mg and 100 mg BID, but the greatest decrease was in subjects receiving 100 mg BID. All subjects in the 100 mg BID dosing group had at least a one log decrease in viral load compared to none in the 3 mg and 10 mg dosing groups and one of four subjects in the 30 mg BID group.

No subject discontinued the study prematurely due to an adverse event. All but one adverse event (an urethral disorder) was graded as mild or moderate. There was no difference in the number or type of adverse events by dose.

In summary, a clear dose response relationship was demonstrated in study ——001. The mean change in plasma HIV RNA increased with increasing enfuvirtide dose and was highest in the 100 mg BID dose group. All four subjects in the 100 mg BID group had at least a one log decrease in HIV RNA compared to one subject of four in the 30 mg BID group and none in the lower dosing groups. The better treatment response in the 100 mg BID group may have been due to the pharmacokinetics of enfuvirtide; enfuvirtide exposure, peak, and trough concentrations were dose dependent and the 100 mg BID dose resulted in the highest plasma concentrations. However, subjects in the 100 mg BID arm may have had a better treatment response compared to other study arms, because all four subjects in the 100 mg BID arm were treatment naïve, while subjects in the other treatment arms were treatment experienced. There were no differences in safety between the four dose groups.

Study ——003
Study ——003 was a randomized, Phase 2 trial comparing the pharmacokinetics, safety, and antiviral activity of enfuvirtide given for 28 days to HIV-infected adults by continuous subcutaneous infusion (CSI) or twice daily subcutaneous injection (SC). Eligible subjects were randomly assigned to one of six treatment arms: 12.5, 25, 50 or 100 mg per day by CSI or 50 or 100 mg by SC injection twice daily. Subjects with signs or symptoms of toxicity or intolerance were allowed to reduce their enfuvirtide dose or change the route of administration. Eligible subjects could be either treatment experienced or treatment naïve but had to have a baseline HIV RNA level of 5,000 copies/ml or greater. Pharmacokinetic measurements were obtained for all subjects on study day 0, at each study visit for subjects receiving enfuvirtide by CSI; and on day 14 for subjects receiving enfuvirtide SC twice daily. Adverse events were assessed at each study visit. Plasma HIV RNA levels were measured at screening, at baseline, on study days 1, 4, 7, 14, 21, and 28, and at follow-up on day 35. Genotypic resistance testing was performed at baseline, on days 14 and 28, and at follow-up.

Seventy-eight subjects enrolled in the study: 13 in each treatment group. The majority of subjects were male (91%) and Caucasian (77%). The mean age was 42.4 years. Most subjects were treatment experienced and had received a mean of 9.7 antiretroviral drugs; one subject in the 25 mg CSI arm was treatment naïve at baseline. The baseline plasma HIV RNA level was similar in all treatment groups and ranged from 4.8 to 5.1 log_{10} copies/ml. The mean baseline CD4 count for all treatment groups was less than 200 cells/mm^3 and ranged from 87.5 to 172.5 cells/mm^3 for each treatment group.

Seventy-eight subjects were randomized to a treatment group, 75 received at least one dose of study drug; three discontinued before receiving study drug. Five subjects (10%) prematurely discontinued the study: two due to injection site reactions, two withdrew

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consent, and one due to protocol violation. Study discontinuations were more common in subjects receiving the highest dose of enfuvirtide (100 mg per day); both subjects who withdrew due to injection site reactions and one subject who withdrew consent were receiving 100 mg daily. Fourteen patients (18%) switched from continuous infusion to twice daily SC injection: 12 due to delivery complications and two due to local reactions.

Pharmacokinetic measurements were dose proportional for the subjects receiving enfuvirtide by subcutaneous injection. The mean $AUC_{(0-12)}$, peak, and trough concentrations on day 14 for the 50 mg BID group were 21374 ng.hr/ml, 2626 ng/ml, and 932 ng/ml, and for subjects receiving 100 mg SC were 36502 ng.hr/ml, 4725.5 ng/ml, and 1413 ng/ml. Dose proportional changes in pharmacokinetic measurements were not observed in the CSI group. The $AUC_{(0-12)}$ (29626 versus 36502 ng.hr/ml) and peak concentrations (3972.5 versus 4725.5 ng/ml) of enfuvirtide were slightly lower in the 100 mg CSI group compared to the SC group.

A decrease in plasma HIV RNA levels from baseline to day 28 was reported in all dose groups. As shown in the table below, subjects receiving enfuvirtide by twice daily SC injection had a better treatment response than those receiving enfuvirtide by CSI.

Table 2: Change from Baseline in Plasma HIV RNA in Study TRI-003

	CSI				SC	
	12.5 mg	25 mg	50 mg	100 mg	50 mg BID	100 mg BID
Mean maximum change	-0.5±0.09	-0.6±0.15	-0.8±0.12	-0.9±0.18	-1.0±0.16	-1.6±0.16
% of subjects with ≥1 log ↓ in RNA	0	12.5%	12.5%	25%	50%	83%

Source: CSR submitted July 16, 2002, Volume 135, page 36.

Among subjects receiving enfuvirtide by SC injection, more subjects receiving 100 mg than 50 mg had a one log or greater decrease in viral load and the mean maximal change in HIV RNA was higher in the 100 mg group. Overall, subjects administering enfuvirtide by twice daily SC injection had a better treatment response and the degree of treatment response correlated with higher dose.

The maximum decrease in HIV RNA was observed between day 7 and day 14. Although HIV RNA levels started to rebound after that, day 28 values were lower than baseline values. Genotypic resistance to enfuvirtide on day 28 was reported in 31 subjects: nine subjects receiving 50 mg SC BID, six receiving 100 mg SC BID, five subjects receiving 25 mg CSI, six subjects receiving 50 mg CSI, and five receiving 100 mg CSI. The waning suppression of HIV RNA by day 28 is typical for subjects receiving

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monotherapy for treatment of HIV infection and was due to the rapid development of resistance.

All study subjects reported at least one adverse event. The most common adverse event was injection site reactions, which were reported in 96% of subjects. The incidence of injection site reactions was similar in all treatment groups. A Grade 3 injection site abscess was reported in one subject receiving 50 mg CSI. Two subjects withdrew from the study because of injection site reactions: one subject (100 mg CSI) with induration, rash, and pain at the site and one (100 mg SC) with rash and pruritis at the site. There was no difference in the number or type of other adverse events between treatment groups.

In summary, in study ----003, subjects receiving enfuvirtide by twice daily injection had a better treatment response. Among subjects receiving enfuvirtide by SC injection, subjects receiving 100 mg BID had a greater decrease in HIV RNA compared to those receiving 50 mg BID. This may have been related to the dose proportional pharmacokinetics observed; the plasma concentration of enfuvirtide was approximately twice as high after 100 mg BID compared to 50 mg BID. Dose of enfuvirtide did not affect the frequency of ISRs; almost all subjects developed injection site reactions regardless of dose. More subjects receiving 100 mg of enfuvirtide twice daily withdrew from the study including two who withdrew due to injection site reactions, suggesting that ISRs may be more severe at higher doses. There did not appear to be any difference in other adverse events by dose.

Study T20-206
Study T20-206, "A Controlled Phase 2 Trial Assessing Three Doses of T20 in Combination With Abacavir, Amprenavir, Ritonavir and Efavirenz in HIV Infected Adults," was a 48 week, open label, controlled, randomized, multi-center, dose-ranging trial of enfuvirtide in HIV-1 infected adults 18 years of age and older. Subjects were protease inhibitor experienced and non-nucleoside reverse transcriptase inhibitor naïve with plasma HIV-1 RNA levels of 400 copies/ml or greater. Subjects were randomized to one of four treatment groups; three groups received enfuvirtide at a dose of 50mg, 75mg or 100mg subcutaneous twice daily plus the background antiretroviral drug regimen (abacavir 300mg BID, amprenavir 1200mg BID, ritonavir 200mg BID and efavirenz 600mg daily QD). and the control group received the background antiretroviral regimen alone.

Virologic failure was defined as less than one log_{10} decrease in HIV RNA from baseline, a viral load greater than 400 copies/ml at four weeks, or as HIV RNA level within 0.5 log10 of baseline after week 8. Subjects assigned to the control group who had evidence of virologic failure were eligible to be randomized to one of the three enfuvirtide groups. Subjects who failed enfuvirtide were permanently discontinued

Seventy-seven subjects were enrolled, and 71 received at least one dose of study drug. The demographic and baseline characteristics of the control and enfuvirtide groups

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were similar; subjects were predominantly male (98%) and Caucasian (73%) with a mean age range of 41-45 years. The baseline CD4 count and plasma HIV-1 RNA level for subjects in each treatment group ranged from 176-314 cells/mm^3 and 3.99-4.25 copies/ml respectively.

Forty-two subjects completed 48 weeks of treatment: 9 of 19 (47%) subjects in the control arm and 20 of 52 (38.5%) in the enfuvirtide arms. Adverse events were the major cause of premature discontinuation from the study. The enfuvirtide 100mg BID group had the most discontinuations: 10 (62.5%), all secondary to injection site reactions or difficulties with injection administration.

Although study T20-206 was not powered to show a difference between the control group and the enfuvirtide groups with respect to HIV RNA viral load reduction or CD4 cell increase, virologic response by treatment group varied slightly as shown in Table 3 below.

Table 3: Proportion of Subjects in Each Treatment Group with Virologic Response

Virologic Endpoint (24 weeks)	Control	Enfuvirtide Arms (BID dose)		
		50 mg	75 mg	100 mg
≤ 400 copies/ml	37%	60%	70%	31%
≤ 50 copies/ml	37%	53%	55%	31%
> 1 log$_{10}$ ↓in HIV RNA	37%	67%	70%	37.5%

Source: CSR submitted July 16, 2002, Volume 80, page 70.

As shown in the table, more subjects receiving either 50 or 75 mg of enfuvirtide twice daily than in the control group had a virologic response at week 24. Ten of the 16 subjects in the 100 mg BID arm prematurely discontinued the study making it difficult to ascertain any treatment effect in that arm. Overall, there were more virologic failures in the control group (15.8%) compared to the group of subjects receiving enfuvirtide (7.6%).

Although more subjects in the enfuvirtide 100 mg BID arm discontinued prematurely because of adverse events, there was no difference in the incidence of adverse events or of serious adverse events between the three enfuvirtide arms. The incidence of injection site reactions was similar in the three arms: 74% of subjects in the 50 mg BID arm reported ISRs, 62% in the 75 mg BID arm, and 76.5% in the 100 mg BID arm.

In summary, three doses of enfuvirtide were studied in T20-206, but the study was not powered to detect differences in efficacy based on enfuvirtide dose, and it is difficult to compare the efficacy or safety of the three doses because of the high rate of premature discontinuations. However, there were more premature study discontinuations due to injection site reactions in subjects receiving 100 mg twice daily suggesting that ISRs may be more severe in subjects receiving higher doses of enfuvirtide. This study had

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not been completed, and therefore, the results were not available when the dose of enfuvirtide for Phase 3 trials was chosen.

Study T20-208

Study T20-208 was a Phase 2, 48 week, multi-center, open-label, sequential cross-over pharmacokinetic, efficacy and safety study of enfuvirtide given to HIV-1 infected adults by subcutaneous injection. Different doses and different formulations of enfuvirtide were studied in T20-208. Subjects were accrued sequentially in one of three cohorts. Subjects in Cohort I and Cohort II were treated with a carbonate buffer formulation of enfuvirtide; subjects in Cohort III received a TRIS formulation. Subjects in all three cohorts received a 50 mg/ml carbonate formulation for 14 days of the study and a 100 mg/ml formulation for the remainder of the study. Subjects in Cohort I and II were treated with enfuvirtide at a dose of 100 mg twice daily, and subjects in Cohort II were treated with 75 mg BID. In addition to enfuvirtide, subjects received an optimized background (OB) regimen of antiretrovirals, chosen by the investigator and the subject, based on the subject's prior history and viral genotypic resistance assessment.

Forty-six subjects were enrolled into the study and received at least one dose of study medication: 22 in Cohort I (enfuvirtide 100mg BID CO3), 12 in Cohort II (enfuvirtide 75mg BID CO3), and 12 in Cohort III (enfuvirtide 100mg BID TRIS). Subjects were predominantly male and Caucasian; the mean age was 42.5 years. Baseline mean plasma HIV RNA levels ranged from 5.2 (Cohort I) to 5.5 (Cohort III) $\log_{10}$ copies/ml. Baseline mean CD4 cell count ranged from 19.6 (Cohort II) to 123.2 (Cohort I) cells/mm^3.

Pharmacokinetic evaluations were performed over a 24 hour period on days 14 and 28. In Cohort I (100 mg BID), the 12 hour AUC (AUC_{12h}) value was 46.2 μg*hr/ml for the 50 mg/ml carbonate formulation and 48.7 μg*hr/ml for the 100 mg/ml carbonate formulation. In Cohort II (75 mg BID), AUC_{12h} was 37.0 μg*hr/ml for the 50 mg/ml carbonate formulation and 34.4 μg*hr/ml for the 100mg/mL carbonate formulation. In Cohort III (100 mg BID), the AUC_{12h} value was 44.7 μg*hr/ml for the 50mg/ml carbonate formulation and 35 μg*hr/ml for the 100 mg/ml TRIS formulation. Post hoc analysis indicated that the 50 mg/ml and 100 mg/ml formulations were bioequivalent, however, the TRIS formulation was not bioequivalent to the 50 mg/ml carbonate formulation.

Subjects in Cohorts I and II had a greater and more rapid virologic response as compared to Cohort III. At week 48 the median decrease in baseline HIV RNA level was −2.97 $\log_{10}$ copies/ml in Cohort I, -3.48 in Cohort II, and −0.87 in Cohort III. In addition by week 48, 59.1% of Cohort I, 66.7% of Cohort II and 16.7% of Cohort III had HIV RNA levels ≤ 400 copies/mL; 40.9% of Cohort I, 41.7% of Cohort II and 16.7% of Cohort III had HIV RNA levels ≤ 50 copies/mL. Virologic failure was more common in Cohort III than either of the other two cohorts: 58.3% compared to 22.7% in Cohort I, 16.7% in Cohort II.

There was no difference in the overall incidence of adverse events, other than injection site reactions, between the study arms. Although, there was no difference in the proportion of subjects with ISRs (all subjects experienced at least one ISR), subjects self-administering the 50 mg/ml of the carbonate formulation reported less pain and discomfort. However, the 50 mg/ml formulation required four injections each day, which is not practical for chronic dosing of enfuvirtide. The incidence of induration, erythema, and pruritis was similar between cohorts, but more subjects in Cohort III (TRIS formulation) reported a Grade 4 ISR (50% compared to 32% in Cohort I and 42% in Cohort III).

In summary, the efficacy of enfuvirtide was clearly influenced by formulation; fewer subjects receiving the TRIS formulation had a virologic response. This was probably due to the lower plasma concentrations observed with this formulation. Efficacy and safety results were similar in subjects receiving either 50 or 100 mg BID of the carbonate formulation; no differences between dose could be determined.

Summary
These four Phase I/2 studies randomized subjects to different daily doses of enfuvirtide. In studies ———001 and———'-003, there was clearly a relationship between dose and antiviral effect. The greatest decrease in plasma HIV RNA was noted with the 100 mg BID dose, which is the proposed dose of enfuvirtide. However, there was no relationship between dose and efficacy in two other studies, T20-206 and T20-208. The results of study T20-206 were difficult to interpret due to the high rate of study discontinuations, particularly in the 100 mg BID treatment group. Doses higher than 100 mg BID might be more efficacious but were not studied, and patient compliance with higher doses would be difficult because of the need for more than two daily injections. In three of the four studies, injection site reactions were more problematic in subjects receiving higher doses of enfuvirtide; in two studies, study discontinuations due to injection site reactions were more common in the 100 mg BID group and in the third injection site reactions appeared to be more severe at higher doses. There was no difference in the incidence or type of other adverse events by dose. In summary, enfuvirtide 100 mg BID appears to be the most efficacious dose studied, but injection site reactions may be more severe at this dose.

2. Drug Interactions

Studies were performed to determine potential drug interactions between enfuvirtide and rifampicin, saquinavir with ritonavir boosting, ritonavir alone, and five different drugs using cytochrome P450 isoenzymes. No interactions were observed between enfuvirtide and rifampicin or saquinavir. There were no drug interactions between enfuvirtide and any of the five drugs using different cytochrome P45 enzymes (CYP1A2, CYP2E1, CYP3A4, CYP2D6, and NAT).

Two studies (T20-503 and NP 16325) demonstrated that enfuvirtide exposure was increased in the presence of ritonavir. Subjects in study T20-503 received enfuvirtide,

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saquinavir, and low dose ritonavir (100 mg BID). After coadministration of these three drugs, peak concentrations of enfuvirtide increased from ‾‾‾‾‾‾ μg/ml, trough concentrations increased from ‾‾‾‾‾‾ μg/ml, and exposure increased from ‾‾‾‾‾‾ ‾‾‾‾ h•μg/ml. However, all of these values were within the 90% confidence interval. In study NP 16325, subjects received enfuvirtide and ritonavir 200 mg BID; plasma concentrations of enfuvirtide were approximately 20% higher when enfuvirtide was administered with ritonavir compared to enfuvirtide alone. No increase in adverse events was associated with the increased plasma concentration of enfuvirtide noted in these studies. In addition, more than 80% of subjects in the Phase 3 clinical trials of enfuvirtide received both enfuvirtide and ritonavir, and no difference in toxicity was noted in these subjects.

In summary, on the basis of these studies, clinically significant drug interactions are unlikely.

IV.   Description of Clinical Data and Sources

A. Overall Data

The analyses of safety and efficacy was based on 24 week data from two 48-week, active controlled Phase 3 clinical trials conducted with over 1000 subjects. Additional data from three pharmacokinetic and safety studies, five drug interaction studies, a rollover study, a Phase 2 controlled clinical trial, and two pediatric studies were also analyzed.

B. Tables Listing the Clinical Trials

Study	Design	Dose and Duration	Total No. of Subjects
Phase 3 Studies			
T20-301	randomized, active control, open-label	90 mg BID SC	512
T20-302	randomized, active control, open-label	90 mg BID SC	501
Phase 1 and 2 Studies			
‾‾‾001	dose escalation	single dose IV of 3, 10, 30 or 100 mg; 3, 10, 30, or 100 mg BID for 14d	17
‾‾‾002	monotherapy followed by combination therapy	50 continuous SC infusion	1

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—003	comparison of route of administration and dose	12.5, 25, 50, or 100 mg by CSI for 28d; 50 or 100 mg BID SC for 28d	78
Phase 2 Studies			
T20-205	rollover safety study for —001, 002, 003	50 mg BID SC for 96 wks	70
T20-206	controlled, randomized, dose-ranging study	50, 75, or 100 mg BIC SC for 48 wks	71
T20-208	sequential crossover study of dose and formulation	CO3 formulation: 50 or 100 mg BID SC Tris formulation: 100 mg BID SC for 48 wks	46
Continuing Access Studies			
T20-210	rollover safety study for subjects on T-1249	90 mg BID SC	31
T20-211	rollover safety study for subjects in Phase 2 studies of enfuvirtide	90 mg BID SC	58
T20-304	rollover safety study for subjects in PK studies	90 mg BID SC	3
Open-label safety study			
T20-305	uncontrolled, open-label	90 mg BID SC	37
Clinical Pharmacology			
T20-501	study comparing PK of SC versus IV enfuvirtide	90 mg BID SC	12
T20-502	drug interaction study	90 mg BID SC	5
T20-504	drug interaction study	90 mg BID SC	12
T20-505	drug interaction study	90 mg BID SC	12
T20-506	study of the influence of injection site on PK	90 mg BID SC	12

C. Postmarketing Experience

There has been no postmarketing experience with enfuvirtide, since it has not marketed in any country.

D. Literature Review

The applicant's literature review consisted primarily of articles discussing current issues in the treatment of HIV-infected patients, particularly the utility of resistance testing in antiretroviral drug selection. Copies of several abstracts describing the results of clinical studies of enfuvirtide were also included.

V. Clinical Review Methods

A. How the Review was Conducted

The clinical review of NDA 21-481 (Fuzeon™) was conducted using volumes 202 to 209 (ISS), volumes 223 to 224 (ISE), volumes 52 to 156 and 182 to 191 (clinical study reports), and electronic SAS transport (JMP) files of the NDA submission. In addition, numerous responses to requests for additional clinical information were reviewed.

Two Phase 3 clinical trials, studies T20-301 and T20-302 were reviewed. Detailed summaries of these studies are included in the Appendix to this review. Safety analyses included review of tables, line listings, and data from JMP files provided by the applicant. Additional data on the increased incidence of pneumonia in subjects receiving enfuvirtide was analyzed using identical methodology. Further safety information derived from pharmacokinetics studies and Phase 2 studies is discussed in the integrated summary of safety section. Recommendations for approval are summarized in the **Conclusions and Recommendations** section.

B. Overview of Materials Consulted in Review

The primary materials consulted included the entire NDA, protocols, and multiple responses to requests for additional information to the NDA. The NDA was submitted in hard copy and in electronic form to the electronic document room; responses to requests for additional information were submitted in hard copy and in electronic form as appropriate.

C. Overview of Methods Used to Evaluate Data Quality and Integrity

The Division of Scientific Investigations (DSI) audited four investigators who participated in study T20-301 (—————————————————————— . The DSI audit found no major deficiencies that indicated compromise of the integrity of the data. All three investigators adhered to pertinent federal regulations of good clinical practices.

D. Were Trials Conducted in Accordance with Accepted Ethical Standards

There was no evidence to suggest that the studies contained in this NDA were not conducted in accordance with accepted ethical standards. All studies appeared to be conducted under good clinical practices.

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E. Evaluation of Financial Disclosure

Pursuant to 21 CFR 54.2(e) the financial certification statement provided by the applicant was reviewed. The applicant requested that investigators and sub-investigators from all studies contained in the NDA disclose proprietary interest or significant equity as defined in the regulations. The applicant has included a list of all investigators and sub-investigators who responded to their request on form 3454.

The applicant disclosed that one sub-investigator in study T20-301 ——————————
—————————————————————— . Another sub-investigator ———————————
had a financial interest in—— in the form of ————— The applicant stated that each of these individuals were sub-investigators in a large double-blind, multi-center study; neither enrolled sufficient numbers of patients to affect the results of the study, and neither was involved in the analysis of the study data. Therefore, the applicant concluded that there was no evidence that these sub-investigators impacted the results of the studies.

VI.   Integrated Review of Efficacy

A. Brief Statement of Conclusions

The antiretroviral activity of enfuvirtide was well documented in multiple clinical trials. In uncontrolled Phase 1 and 2 studies of enfuvirtide subjects experienced decreases in plasma HIV RNA levels after treatment with enfuvirtide as monotherapy or as part of a combination of antiretroviral drugs. Studies T20-301 and T20-302 were the only Phase 3 randomized, controlled trials of enfuvirtide. In these two studies, subjects with advanced HIV disease and substantial prior exposure to antiretroviral therapy were randomized to either enfuvirtide plus an optimized background regimen or an optimized background regimen alone. Subjects receiving enfuvirtide in addition to the optimized background regimen had a further decrease in HIV-1 viral load of 0.846 log10 copies/ml compared to optimized background alone (p<0.0001). In addition, subjects receiving enfuvirtide plus an optimized antiretroviral regimen had a statistically significant increase in CD4 count at 24 weeks compared to subjects receiving an optimized background regimen alone.

B. General Approach to Review of the Efficacy of the Drug

The clinical program to support the efficacy of enfuvirtide for treatment of HIV-infection in combination with other antiretroviral drug is comprised of two Phase 3 clinical trials. All Phase 1 and Phase 2 trials were also reviewed. Efficacy results from selected Phase 1 and Phase 2 trials are described in Section III of this review. The detailed reviews of the two Phase 3 clinical trials are included in Appendix B.

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Clinical Review Section

C. Detailed Review of Trials by Indication

Detailed reviews of the Phase 3 clinical trials are included in Appendix B of this review.

D. Efficacy Conclusions

Enfuvirtide is indicated for the treatment of HIV-infection in treatment experienced patients with ongoing viral replication. This indication is supported by two large, randomized, controlled Phase 3 studies. Enfuvirtide was clearly biologically active in both Phase 3 clinical trials that each used endpoints previously accepted by FDA. In these studies, subjects receiving enfuvirtide had a statistically significant decrease in plasma HIV levels from baseline to week 24 relative to an active control group. Different sensitivity analyses confirmed this robust effect, as did analyses of all secondary endpoints.

VII. Integrated Review of Safety

A. Brief Statement of Conclusions

There are several significant safety concerns with enfuvirtide. The most common adverse events associated with enfuvirtide were injection site reactions, which were observed in almost all study subjects. Common signs and symptoms of ISRs included pain or discomfort, erythema, induration and nodules. ISRs begin almost immediately with onset of therapy and continued to recur throughout the study period. Since individual ISRs often lasted for several days, subjects usually had more than one ISR at any given time during the study. Despite these reactions, only 4% of subjects discontinued therapy in the Phase 3 studies due to ISRs. In addition, complications of ISRs were rare with only 1% of subjects reporting infections at the injection site.

Hypersensitivity/allergic reactions were reported in less than 1% of subjects receiving enfuvirtide with recurrence on rechallenge in some cases. Signs and symptoms of hypersensitivity reaction included fever, rash, nausea, vomiting, hypotension, and increased transaminases. There were no deaths due to a hypersensitivity reaction. Rare cases of immune complex mediated disease, i.e., glomerulonephritis, and Guillain Barre Syndrome, were observed.

In Phase 3 studies, bacterial pneumonia was reported in more subjects receiving enfuvirtide than in those receiving the active control. The reason for this increase was unclear; it may have been related to the study design or to an unusually low incidence of pneumonia in the control arm. The incidence of pneumonia in subjects receiving

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