enfuvirtide was similar to that reported in the scientific literature. However, the possibility of an immunosuppressive effect with enfuvirtide cannot be excluded.

Although these safety concerns are substantial, the benefits of using enfuvirtide outweigh the risk. Safety information and risk management concerns are included in the package insert and in all patient education materials. Both hypersensitivity reactions and pneumonia are 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 may be associated with considerable morbidity; therefore, ISRs are also included in the Warnings section.

B. Description of Patient Exposure

A Safety Update Report to this New Drug Application was submitted in November 2002. At the cutoff date for this report, a total of 1541 subjects had received at least one dose of enfuvirtide. Of these, 1401 had received enfuvirtide at the dose proposed for labeling (90 mg BID in adults and 2.0 mg/kg BID for children 6 years of age and older). A total of 913 subjects had received enfuvirtide for at least 24 weeks, and 569 subjects had received enfuvirtide for at least 48 weeks.

A total of 1013 subjects were enrolled in the two Phase 3 clinical trials of enfuvirtide; 673 were randomized to receive enfuvirtide plus an optimized antiretroviral regimen and 340 to receive the optimized background regimen only. Study T20-301 was conducted at 48 study sites in North America and Brazil. Study T20-302 was conducted at 67 study sites in Western Europe and Australia. The majority of subjects in these two trials were male (90%) and Caucasian (89%). Most subjects enrolled in Phase 1 and 2 studies of enfuvirtide were also male and Caucasian. Three clinical pharmacology studies with a total of 37 subjects were conducted at a single study site in Thailand; all subjects were Asian/Pacific Islanders and 57% were female.

C. Methods and Specific Findings of Safety Review

Studies T20-301 and T20-302 are the only randomized, controlled Phase 3 studies of enfuvirtide. The majority of subjects who participated in studies of enfuvirtide were treatment experienced and many had advanced disease, therefore, the clinical course was often complicated by subjects' underlying HIV disease and toxicities associated with the use of concomitant drugs. Because of the complicated patient population, the integrated summary of safety will primarily focus on the two Phase 3 clinical trials of enfuvirtide to allow comparison of adverse events observed in subjects receiving enfuvirtide to subjects receiving an active control.

Studies T20-301 and T20-302 were both randomized, open-label, active controlled studies of enfuvirtide 90 mg administered twice daily by subcutaneous injection; they

had similar study designs, patient selection criteria, and analyses. Subjects in study T20-302 were required to have three months of prior treatment with a drug from each antiretroviral class compared to six months experience in T20-301, and subjects in T20-302 must have had prior treatment with or resistance to one protease inhibitor compared to two protease inhibitors in study T20-301. 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. FDA safety analysis was done separately for each study. If a possible safety signal was detected in one study, the second study was examined for possible confirmation; the similarity in study design of these two studies allowed for the direct comparison of results from both trials. Therefore, the FDA safety analysis for both studies are presented together.

1. Deaths

The causes of death for all subjects who died during the first 24 weeks of studies T20-301 and T20-302 are listed in Table 4 below. This includes deaths that occurred during treatment with enfuvirtide or within 28 days of stopping enfuvirtide.

Table 4: Cause of Death in Studies T20-301 and T20-302

Cause of death (No. of subjects if > 1)	Treatment Arm
advanced AIDS	enfuvirtide + OB
bronchopneumonia (2)	enfuvirtide + OB
cardiac failure	enfuvirtide + OB
cytomegalovirus infection	enfuvirtide + OB
Guillain Barre syndrome	enfuvirtide +OB
pancreatitis	enfuvirtide +OB
sepsis (2)	enfuvirtide + OB
suicide	enfuvirtide + OB
cardiomyopathy	Switch[1]
sepsis	Switch[1]
advanced AIDS (2)	OB
AIDS encephalopathy	OB
lymphoma	OB
toxoplasmosis	OB

Source: Death datasets from July 16, 2002 submission.

Subjects in the OB group who experienced virologic failure were allowed to "switch" to a enfuvirtide containing antiretroviral regimen.

As stated in the table, there were 10 deaths in subjects who received enfuvirtide + OB, five in the OB group, and 2 in switch subjects during the first 24 weeks of the study. Switch subjects were those subjects who were originally randomized to the OB group but switched to an enfuvirtide containing regimen after experiencing virologic failure.

After correcting for the 2:1 randomization, there was no difference in the mortality rate between the two groups. Two deaths in enfuvirtide + OB subjects were attributed to enfuvirtide: one due to Guillain Barre syndrome and one to suicide. The investigator attributed the development of Guillain Barre to the use of enfuvirtide because of the possibility that it was the result of immune complex formation. The subject who committed suicide had a history of depression and was described by the site investigator as having expressed considerable anxiety about self-injection and injection site reactions. There were five deaths due to infection in subjects receiving enfuvirtide: three with sepsis and two with bronchopneumonia.

Deaths in the optimized background group were due to advanced HIV disease (2), lymphoma, toxoplasmosis, and AIDS encephalopathy.

There were five deaths in Phase 1 and 2 studies. The deaths were all in rollover studies providing continued access to enfuvirtide after participation in Phase 1 studies or in clinical pharmacology studies. Causes of death were aspergillus pneumonia, recurrent *Pseudomonas* pneumonia, pneumonia, soft tissue carcinoma, endstage AIDS, and progressive multifocal leukoencephalopathy.

In the Phase 3 studies, the mortality rate was similar between the enfuvirtide group and the control group. There were five additional deaths in subjects receiving enfuvirtide as part of a rollover study. The majority of deaths were due to advanced HIV disease or conditions associated with advanced HIV disease and its treatment. Subjects on enfuvirtide who died of pneumonia or sepsis had profound immunosuppression and often had coexisting diseases at the time of death; it is unlikely that immunosuppression due to enfuvirtide was an important factor in these subjects' disease course.

2. Other Serious Adverse Events

In the two Phase 3 studies, serious adverse events were reported in 25% of subjects in the enfuvirtide + OB arm and in 23% of subjects in the OB arm during the first 24 weeks of the studies. Adverse events that were fatal or life threatening, resulted in disability, required hospitalization, or prolonged hospitalization as well as Grade 4 laboratory values were counted as serious adverse events. Serious adverse events observed in at least 0.5% of subjects (n=3) receiving enfuvirtide in Phase 3 studies are shown in the table below.

Table 5: Proportion of Subjects with Serious Adverse Events in Phase 3 Studies of Enfuvirtide

Serious Adverse Event	Enfuvirtide + OB	OB
↑ CPK	2.1%	3.0%
↑ GGT	2.1%	2.1%
pancreatitis	1.8%	0.6%
anemia	1.7%	0.9%
neutropenia	1.7%	2.4%
↑ lipase	1.4%	0.6%
pneumonia	0.8%	0.3%
pyrexia	0.8%	1.8%
↑ amylase	0.6%	0.3%
↑ ALT	0.5%	0.3%
↑ AST	0.5%	0
cellulitis	0.5%	0.3%
bronchopneumonia	0.5%	0
sinusitis	0.5%	0
myocardial infarction	0.5%	0.3%
hepatitis	0.5%	0

Source: ISS from July 16, 2002 submission, page 113.

As seen in this table, many of the serious adverse events were Grade 4 laboratory abnormalities; the most common serious adverse events in both the enfuvirtide + OB group and the OB group were increased CPK and GGT.

Pancreatitis was more reported more commonly as a serious adverse event in subjects receiving enfuvirtide, as were increased lipase and amylase. In study T20-301, 11 subjects receiving enfuvirtide + OB developed pancreatitis; seven required hospitalization and two of these discontinued enfuvirtide because of pancreatitis. Pancreatitis was reported in four subjects in the OB group; all four required hospitalization. However, there was not an increase in the incidence of pancreatitis in enfuvirtide recipients in study T20-302 (7 subjects in the enfuvirtide + OB arm versus 4 subjects in the OB arm). There were no cases of pancreatitis in subjects switching from the OB group to an enfuvirtide containing regimen in either study. The mean amylase value at week 24 was similar for both treatment groups (83 U/L in the enfuvirtide + OB group and 82 U/L in the OB alone group), but the mean lipase value at week 24 was slightly higher in the enfuvirtide + OB group compared to the OB group (69 U/L in the enfuvirtide + OB group and 55 in the OB alone group). The mean change in lipase from baseline to week 24 was +17.7 for the enfuvirtide + OB group and +0.86 for the OB group. Other antiretroviral drugs, particularly didanosine and stavudine have been associated with pancreatitis; however, there was no difference in the use of either didanosine or stavudine in the two treatment groups. In summary, the incidence of pancreatitis was slightly higher in one of the two studies but not in the other and higher lipase values were observed in enfuvirtide recipients in both studies. Although the

overall risk of pancreatitis appears to be low in subjects receiving enfuvirtide, an increased risk of developing pancreatitis in patients receiving enfuvirtide cannot be excluded.

Pneumonia was reported as a serious adverse event in five subjects receiving enfuvirtide, bronchopneumonia in three, and lower respiratory tract infections in two compared to one subject with pneumonia in the OB arm. The increased incidence of pneumonia in subjects receiving enfuvirtide is discussed in Section VII.C.4.

Increased ALT, increased AST and hepatitis were each reported in three subjects receiving enfuvirtide. However, the mean bilirubin value at week 24 for subjects in both the enfuvirtide + OB and OB arms in study T20-301 was 0.65 mg/dL; the mean bilirubin values at week 24 in study T20-302 were similar (10.8 umol/L in the enfuvirtide + OB group and 9.3 umol/L in the OB group). In addition, mean ALT and AST values were higher for subjects in the OB group at week 24 in both studies. Therefore, there is no evidence of obvious hepatic toxicity associated with enfuvirtide use.

Depression was reported as a serious adverse event in two subjects receiving enfuvirtide and suicide attempt was reported in two. This compared to no serious AEs of depression or suicide attempt in the OB group. One subject with a history of depression had anxiety, which was attributed to self-administration of enfuvirtide and to ISRs, and committed suicide; his healthcare provider judged this event as drug related. Six subjects receiving enfuvirtide discontinued the study due to depression and one due to stress. There was no difference in efavirenz use between the two treatment groups. Although enfuvirtide itself could cause anxiety or depression, it is more likely that twice daily self injection of enfuvirtide and the presence of multiple ISRs are stressful for subjects, particularly for subjects with few other treatment options and advanced HIV disease.

Three subjects reported serious adverse reactions suggestive of hypersensitivity to enfuvirtide. These included one subject with Guillain Barre syndrome, one with an allergic reaction (fever, vomiting, and rash), and one with immune complex glomerulonephritis. Two of the three were rechallenged with enfuvirtide and again developed symptoms of an hypersensitivity reaction. Hypersensitivity reactions with enfuvirtide are discussed further in Section VII.C.4.

Serious adverse events were reported in 7 of 93 subjects participating in the Phase 1 and 2 studies of enfuvirtide ([redacted]001, [redacted]-002, [redacted]-003). The only serious adverse event that was judged by the investigator to be related to enfuvirtide was an injection site abscess. Other serious adverse events reported in these studies were urethral disorder, gout, catheter site infection, anemia, and leukopenia.

Thirty-nine percent (65/168) subjects in Phase 2 studies of enfuvirtide (T20-205, T20-206, T20-208) experienced serious adverse events. Serious adverse events reported in more than one subject included pneumonia, sepsis, neutropenia, abnormal thinking,

and hypersensitivity reaction. Primary immune complex disease was reported in one patient in study T20-208 who developed chills, malaise, shortness of breath, and chest discomfort. The risk of hypersensitivity reactions and immune complex disease with enfuvirtide is discussed in Section VII.C.4. An abdominal wall abscess at an enfuvirtide injection site was reported in a single subject; ISRs and complications of ISRs are also discussed in Section VII.C.4.

Although serious adverse events were reported in one-fourth of subjects receiving enfuvirtide in Phase 3 clinical trials, SAEs were reported in a similar incidence in the control group. The most commonly reported serious adverse events were Grade 4 laboratory abnormalities; the incidence of most of these abnormalities was low and similar to that noted for subjects in the control arm. Pneumonia was reported more often in subjects receiving enfuvirtide + OB compared to OB alone, and patients receiving enfuvirtide must be educated about this risk, which is prominently stated in the package insert and the patient package insert. Hypersensitivity reactions were reported in Phase 2 and 3 studies of enfuvirtide; this risk is also mentioned in the Warnings section of the package insert and in the patient package insert. Finally, abscesses at the enfuvirtide injection site were reported. Patients receiving enfuvirtide will require extensive education about proper injection techniques and recognition of complications.

3. Adverse Events Leading to Study Discontinuation

Of the 1541 subjects who received at least one dose of enfuvirtide in any clinical trial, 115 discontinued the study prematurely due to an adverse event other than an injection site reaction. In studies T20-301 and T20-302, the rate of study discontinuation due to an adverse event was higher in the enfuvirtide + OB group (7.2% or 9.8 patients/100 patient years) than in the OB group (3.0% or 6.7 patients/100 patient years). The most common reason for study discontinuation in subjects receiving enfuvirtide was an injection site reaction; 14 subjects discontinued in the first 24 weeks of the study due to an ISR and another three withdrew due to problems with self-injection. The most common reason for discontinuation (seven subjects) after the initial 24 weeks of these studies was also injection site reactions. An additional ten subjects discontinued after 24 weeks because of difficulties with self-administration by injection such as being tired of injecting, finding it too demanding, or lack of sites to inject.

The second most frequent adverse events leading to study withdraw were gastrointestinal signs or symptoms, including vomiting and nausea in the enfuvirtide + OB group, and vomiting, nausea, and diarrhea in the OB group. Seven subjects discontinued enfuvirtide because of depression, versus no subjects in the OB arm discontinued due to depression. Several subjects in the enfuvirtide + OB arm discontinued because of infectious events (sepsis-3, pneumonia-1); no subjects in the OB arm discontinued the study due to sepsis or pneumonia. Three subjects receiving enfuvirtide discontinued after hypersensitivity reactions; no subjects in the OB arm discontinued due to a hypersensitivity reaction. Other reasons for premature study

discontinuations that were reported in subjects in the enfuvirtide + OB arm but not the OB arm included rash or dermatitis (3), pancytopenia (2), and hepatitis (2).

The overwhelming majority of subjects in the OB arm either discontinued due to virologic failure or stopped treatment because of insufficient therapeutic response (118/169 or 70%).

Two subjects in the initial Phase I/2 studies of enfuvirtide (-001, -002, and -003) prematurely withdrew from the study due to an injection site reaction; three subjects in the Phase 2 studies withdrew due to ISRs. Another 15 subjects in these studies prematurely discontinued a study due to an adverse event; the most common reasons were rash (4) and nausea (3).

The most common reason for subjects receiving enfuvirtide to prematurely discontinue a study was an injection site reaction. Subjects also discontinued because of the difficulties associated with twice daily self-injection. Although the overall rate of study discontinuation due to ISRs was low (4%), patients will require intense education on injection technique, recognition of typical signs and symptoms of ISRs, and recognition of complications of ISRs.

4. Other Significant Adverse Events

Injection site reactions

Local injection site reactions (ISRs) were the most common adverse events associated with enfuvirtide treatment. During the Phase 3 trials, ISRs were assessed at each study visit using a standardized tool that graded the overall reaction, defined by the degree of pain and discomfort, as well as individual signs and symptoms. Virtually all subjects (98%) had an ISR during the first 24 weeks of the study. The large majority of subjects reported an ISR at the first study visit (86%), and ISRs continued to be reported throughout the study. The incidence of subjects with an ISR at study visits from week 2 to week 24 ranged from 60% to 74.5%. Most ISRs (95%) were associated with pain or discomfort; 9% of subjects needed prescription analgesics or narcotics for the pain. Individual signs and symptoms were common: erythema (89%), induration (89%), nodules or cysts (76%), pruritis (62%), and ecchymosis (48%). The erythema was often extensive and approximately 30% of subjects had erythema > 5 cm in diameter. Almost one-half of subjects had Grade 3 or 4 induration (≥ 25 mm). Approximately 25% of subjects had nodules or cysts that were greater than or equal to 30 mm in size. Pruritis and ecchymosis were usually mild (85% with Grade 1 pruritis and 87% with Grade 1 or 2 ecchymosis). Most subjects had one to five ISRs at any point in time. Individual ISRs usually lasted less than 7 days. The severity of ISRs and of individual signs and symptoms did not appear to increase over time.

Thirteen subjects (1.5%) in studies T20-301 and T20-302 reported an ISR as an adverse event (28 individual AEs). Individual adverse events included 14 episodes of cellulitis, three abscesses, and one granuloma at the injection site. One subject

developed urticaria at the injection site. Other ISRs were reported as adverse events due to increased pain, prolonged duration, and severe pruritis. Two hundred seven subjects received treatment for an ISR. Potential treatments of ISRs were not described in the study protocol, and the treatments used were not included in the study report.

In the Phase 3 studies, there was no association of the severity of signs and symptoms of ISRs with gender, race, age, or body mass. Severity of signs and symptoms was associated with the enfuvirtide formulation in study T20-208. All subjects in that study reported at least one ISR, but pain, erythema and pruritis were reported less commonly with the carbonate formulation, which will be the marketed formulation and which was used in all other studies, than the TRIS formulation. Subjects reported less pain with the 50 mg/ml carbonate formulation than the 100 mg/ml, but use of the 50 mg/ml would require two injections per dose or four per day, which is not practical for the chronic use of enfuvirtide.

Four percent of subjects withdrew from a Phase 3 study because of ISRs. An additional 15 subjects discontinued due to problems with self-injection such as being tired of injecting and difficulties with injecting; if these subjects are included, 42 subjects (6.3%) of subjects in the Phase 3 trials discontinued due to problems related to the injection of enfuvirtide.

The percentage of subjects reporting ISRs or prematurely discontinuing from Phase 1 and 2 studies was lower than in Phase 3 studies, most likely due to the shorter treatment courses in most Phase 1 and 2 studies. In addition, different assessment tools were used to describe the signs and symptoms of ISRs in Phase 1 and 2 studies, so it is difficult to compare the incidence of ISRs and their signs and symptoms in all studies of enfuvirtide. ISRs were reported commonly in all studies, with 80% of subjects in Phase I/2 studies, 83% in Phase 2 studies, and 81% in clinical pharmacology studies reporting ISRs. Two subjects in Phase 1 and 2 studies developed an abscess at the injection site. Two subjects (2.2%) in the Phase I/2 studies and three (1.8%) in the Phase 2 studies withdrew from the study due to an ISR. The signs and symptoms of ISRs were similar in all studies: induration, nodules, pain, and erythema.

In study NV16471, tissue samples were obtained by excisional biopsy from the injection sites of seven subjects administering enfuvirtide. Four subjects had nodules, one had erythema without nodules, one had induration, and one had no clinically observable reaction. Tissue samples were assessed using light microscopy after hematoxylin and eosin staining, immunohistochemical staining, and molecular methods. An inflammatory infiltrate consistent with a hypersensitivity reaction was observed in all samples. The infiltrates included eosinophils, histiocytes, rare lymphocytes, and rare plasma cells. There was focal pallor and some fragmentation of the connective tissue in all subjects. All samples were positive for enfuvirtide by immunoperoxidase staining, and the inflammatory and collagen changes were greatest in the areas of enfuvirtide

deposition. There was no relation between the clinical reaction and the degree or localization of inflammation.

In summary, injection site reactions are by far the most common adverse events associated with the use of enfuvirtide and were seen in almost all subjects in Phase 3 studies of enfuvirtide. The ISRs were often substantial with large areas of induration, erythema, or nodules or with pain. However, subjects usually continued enfuvirtide in spite of ISRs. Complications of ISRs were uncommon, and permanent sequelae or long-term complications from ISRs did not occur.

ISRs are virtually certain to occur in patients who receive 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 studied in Phase 3 trials (and under less controlled conditions than in clinical trials), infectious complications are likely to be seen in a greater proportion of patients.

Hypersensitivity reactions

Hypersensitivity reactions associated with enfuvirtide were identified by the applicant as the Phase 3 studies were ongoing. Accordingly, on November 13, 2002, the applicant issued a letter to enfuvirtide study investigators describing hypersensitivity reactions. In the NDA submission, 13 subjects receiving enfuvirtide reported 17 hypersensitivity reactions in study T20-301: anaphylaxis (2), drug hypersensitivity (9), and hypersensitivity (6). All but one of these reactions was attributed to a study drug other than enfuvirtide. The remaining subject was a 38 year old white male who developed fever, rash, and vomiting on day 8. All study drugs were stopped at that time. Although symptoms subsequently recurred on rechallenge with enfuvirtide, symptoms also recurred when the OB regimen alone was restarted later. There were 11 hypersensitivity reactions in subjects receiving enfuvirtide in study T20-302; seven of these were attributed to study drugs other than enfuvirtide. Limited descriptions are available for the specific events in three of the four remaining subjects: one subject developed facial, mouth, and eyelid edema with fever, vomiting and diarrhea on day 30; one subject developed rash and fever on day 28, and one developed pruritis and erythema.

Other adverse events possibly related to immune complex formation were reported. One subject in study T20-301 developed type 1 membranoproliferative glomerulonephritis. Another subject in T20-301 developed Guillain Barre syndrome, and subsequently died of respiratory failure. The investigators attributed both of these adverse events to enfuvirtide.

The risk of a hypersensitivity reaction associated with enfuvirtide is small (<1% of subjects in Phase 3 studies), but definite and may recur on rechallenge. No fatal

hypersensitivity reactions were reported in these studies. Healthcare providers and patients must be aware of this risk before starting treatment with enfuvirtide. It is also possible that the use of enfuvirtide is associated with the formation of immune complexes that manifest as diseases such as glomerulonephritis or Guillain Barre syndrome. These types of adverse events occurred rarely in the studies reported in this NDA. Although a cause and effect relationship with enfuvirtide use is difficult to prove, it cannot be ruled out.

Bacterial pneumonia

The datasets from studies T20-301 and T20-302 were examined to assess the risk of bacterial infection due to daily injection in subjects who were immunocompromised from their underlying disease. Rates of all infections in studies T20-301 and T20-302 were examined as well as the rate of bacterial infections. There was no overall increase in the number of subjects in the enfuvirtide + OB group with any infection compared to the OB group, but there was an increase in the number of subjects in the enfuvirtide group with bacterial infections. Results for both studies are shown below in Table 6.

Table 6: Number of Study Subjects with Any Infection and with Bacterial Infections in Studies T20-301 and T20-302

	Study T20-301			Study T20-302		
	Enfuvirtide + OB	OB	Switch	Enfuvirtide + OB	OB	Switch
Any infection	199	90	29	185	92	43
Bacterial infections	31	6	6	37	9	4

Source: Adverse event datasets from July 16, 2002 submission.

There is still the appearance of an increase in the number of study subjects with bacterial infections in both studies after accounting for the 2:1 randomization. The specific types of bacterial infections were further identified and there appeared to be an increase in the incidence of pneumonia, abscess, cellulitis, sepsis, and localized infections in subjects receiving enfuvirtide. Because 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, 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. Therefore, the incidence of bacterial infections was adjusted for study drug exposure, and the results are shown in the table below.

Table 7: Incidence of Infection Corrected for Exposure for Studies T20-301 and T20-302 (Events per Patient Years)

	Enfuvirtide + OB	OB	Switch
All bacterial infections	18.56	18.34	23.00
Pneumonia	4.68	0.61	4.60
Sepsis	1.87	1.22	1.97

Source: January 29, 2003 submission

As shown in this table, the incidence of all bacterial infections was similar between the enfuvirtide + OB and OB groups. However, the incidence of pneumonia remained elevated in subjects receiving enfuvirtide + OB compared to those receiving OB alone, and the incidence of sepsis also remained slightly increased. Incidence of all other individual bacterial infections was either the same between the two groups or higher in the OB group after correction for exposure.

In order to further define the scope of this finding, we examined risk factors for the development of bacterial pneumonia and at the associated morbidity and mortality. Subjects who developed pneumonia commonly had risk factors such as profound immunosuppression, current or past smoking, or history of lung disease. Ninety-one percent had at least one risk factor, and 13 of 41 had at least three. The presence of known risk factors for pneumonia are shown in Table 8.

Table 8: Incidence of Risk Factors for Bacterial Pneumonia

	Enfuvirtide + OB (n=41)	**OB (n=1)**	**Switch (n=10)**
CD4 count < 50 at baseline	25 (61%)	1 (100%)	6 (60%)
CD4 count <50 at onset	11 (27%)	0	2 (20%)
Antibiotic use for prophylaxis	30 (73%)	1 (100%)	7 (70%)
Smokers	29 (71%)	1 (100%)	7 (70%)
Non-smoker	12 (29%)	0	3 (30%)
IVDU	6 (14.6%)	0	0
Previous lung disease	21 (51%)	0	6 (60%)

Source: February 5, 2003 and February 14, 2003 submissions.

Immunosuppression as evidenced by low CD4 counts was common in subjects with pneumonia; 81% of enfuvirtide subjects with pneumonia had CD4 counts less than 200 cells/mm^3 at baseline and 61% less than 50 cells/mm^3. Twenty-three subjects (56%) had a CD4 count less than 200 at the time of pneumonia onset; 27% of subjects with pneumonia had a CD4 count less than 50 cells/mm^3 at onset of pneumonia. A higher percentage of subjects with pneumonia had a history of past or current smoking than those subjects who did not develop pneumonia (71% compared to 59%). Antibiotic use for prophylaxis was approximately 20% higher in subjects with pneumonia than in those

without pneumonia. Not surprisingly, the most frequently used antibiotic was trimethoprim/sulfmethoxazole. A higher incidence of pneumonia was observed in enfuvirtide recipients with a history of intravenous drug use (11%) compared to non-use (6%). Finally, there was an increased incidence of pneumonia in subjects with a history of lung disease than those without; 7% of subjects with a history of lung disease developed pneumonia compared to 5% without previous lung disease.

After further analyses of laboratory results, there was no difference in the incidence of treatment-emergent neutropenia or lymphopenia between subjects in the two treatment groups. Grade 3 or 4 neutropenia was observed in 5.9 subjects per 100 patient years in all enfuvirtide recipients and in 12.9 subjects per 100 patient years in the OB group. Grade 3 or 4 decreases in white blood count were more common in the OB group (9.8 subjects/100 patient years) than in enfuvirtide recipients (3.8 subjects/100 patient/years).

The causative organism was isolated in only a minority of cases of pneumonia. There was no predilection for any specific organism or class of organisms. The only organisms isolated in more than one subject with pneumonia were pseudomonas (3) and pneumococcus (2).

Twenty-seven of the 50 episodes of pneumonia in enfuvirtide recipients were reported as serious. Three subjects died. All three of these subjects were profoundly immunosuppressed with CD4 counts less than 50 cells/mm^3 at baseline and at the time of pneumonia onset. All three had concurrent illnesses that contributed to the severity of their illness: one with lymphoma and history of pseudomonas pneumonia, one with aspiration pneumonia after a seizure, and one with neutropenia, Kaposi's sarcoma, and esophageal candidiasis.

The reason for the increased incidence of pneumonia in enfuvirtide recipients is not known. Since enfuvirtide is a new molecular entity and the first drug of the new class of entry inhibitors, the possibility that it is immunosuppressive must be considered. An interaction of enfuvirtide with the N-formyl peptide receptor has been described; this interaction could theoretically lead to a decrease in IL-12 levels. Patients with IL-12 deficiency typically have a increased susceptibility to infection with intracellular pathogens. When the incidence of infection due to intracellular pathogens such as mycobacteria, Listeria, and Salmonella was analyzed, there was no difference between the two treatment groups. There was no evidence of other types of immunosuppression in subjects receiving enfuvirtide. Both neutropenia and lymphopenia were observed more commonly in the OB group than the enfuvirtide + OB group. There was no predisposition to infection with any one microorganism or class of organisms. There was a significantly greater increase in CD4 counts in the enfuvirtide + OB arm. After analysis of the data, there was no evidence for any specific, known type of immunosuppression.

It is possible that the increased rate of pneumonia in the enfuvirtide + OB arm was a consequence of the study design. Subjects in the OB arm who experienced virologic failure could discontinue the study and switch to a enfuvirtide containing regimen any time after week 8 while subjects in the enfuvirtide + OB arm who experienced virologic failure could choose to remain on enfuvirtide. Therefore, only OB subjects with a good virologic and immunologic response to treatment remained on study. Since these subjects were benefiting from their study drugs, their risk of pneumonia was lower. In support of this, subjects who remained on their OB regimen for the entire 24 weeks had a 2.16 log decrease in plasma HIV RNA levels and a 83 cell increase in CD4 count.

An alternative but related explanation for the increased incidence of pneumonia in the enfuvirtide + OB arm is that the number of subjects receiving enfuvirtide with pneumonia may more closely reflect the true incidence of pneumonia in an HIV-infected population while the incidence of pneumonia in the OB arm was abnormally low and not representative. This hypothesis is supported by a literature review provided by the applicant. The applicant summarized six large epidemiologic studies with rates of bacterial pneumonia ranging from 5.5 to 17.9 episodes per 100 patient years. The incidence of pneumonia was even higher in HIV-positive patients with a history of intravenous drug use or those with low CD4 counts (<100 cells/mm^3). Although most of these studies predate the use of protease inhibitors, one study found that the rate of pneumonia was 7.7 cases per 100 patient years in HIV-infected subjects receiving highly active antiretroviral therapy. The rate of pneumonia in subjects receiving enfuvirtide in studies T20-301 and T20-302 is consistent with these studies. The incidence of pneumonia in the OB arm was unusually low, 0.61 cases/100 patient years, and lower than that reported in the literature.

In summary, an increase in bacterial pneumonia was observed in subjects receiving enfuvirtide in both Phase 3 clinical trials. The development of pneumonia was associated with known risk factors such as low CD4 counts, previous lung disease, and smoking. The risk of developing pneumonia did not increase over time. There was no increase in mortality or in AIDS defining events for subjects receiving enfuvirtide. Finally, the reason for the increased incidence of pneumonia in subjects receiving enfuvirtide is unknown but may be related to study design or a statistical abnormality instead of to enfuvirtide itself. 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.

5. Laboratory findings

In Phase 3 studies, laboratory values were analyzed for mean and median change from baseline to week 24 and for proportion of subjects with new Grade 3 or Grade 4 laboratory abnormalities. Treatment-emergent Grade 3 or 4 abnormalities in amylase (7% vs. 4%) and lipase (8% vs. 5%) were reported by a higher percentage of subjects in

the enfuvirtide + OB group compared to the OB group. The incidence of treatment-emergent eosinophilia in studies T20-301 and T20-302 was 11% in enfuvirtide + OB subjects and 2% in OB subjects, but it did not appear to correlate with any clinical outcome. specifically hypersensitivity reactions or severe ISRs.

6. Human reproductive data

Two pregnancies occurred in enfuvirtide clinical trials: one in the enfuvirtide + OB arm and one in the OB arm of study T20-302. Both pregnancies were terminated.

7. Overdose experience

One subject missed a dose of enfuvirtide and injected two doses (180 mg) at the same time. No adverse effects were noted.

8. Accidental needle stick injuries

One accidental needle stick injury to a HIV-uninfected care giver was reported during the clinical trials of enfuvirtide. The care giver received post-exposure prophylaxis; no follow-up information was available. The risk of needle stick injuries will be decreased by the use of safety syringes with retractable needles and of sharps containers for needle disposal, which will be dispensed with every prescription of enfuvirtide. The risk of needle stick injuries are addressed in both the package insert and the patient package insert. It is imperative that both patients and care givers receive extensive education about the safe administration of enfuvirtide and the safe disposal of used needles.

D. Adequacy of Safety Testing

Twenty four week data was submitted from two large Phase 3 clinical trials to support the safety and efficacy of enfuvirtide in combination with other antiretroviral drugs to treat HIV-1 infection. Forty-eight week data from these trials will be submitted for traditional approval of enfuvirtide. All subjects in these trials received adequate monitoring and follow-up for determination of safety and efficacy.

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 any increased risk of pneumonia in animal models. *In vitro* studies of possible mechanisms of enfuvirtide immunosuppression are also planned.

E. Summary of Critical Safety Findings and Limitations of Data

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.

There was a relative increase in the incidence of bacterial pneumonia for subjects receiving enfuvirtide versus control subjects in both Phase 3 studies; however, the significance of this finding is uncertain. The increased incidence seen in subjects randomized to enfuvirtide may have been due to the study design used in both Phase 3 studies, or 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.

Both hypersensitivity reactions and pneumonia are 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 are also included in the Warnings section.

It is essential that patients initiating treatment with enfuvirtide be carefully educated how to self-administer drug. The applicant has developed extensive patient and professional educational materials to address the challenges faced by enfuvirtide, and these are essential for the safe use of enfuvirtide. 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. All of these materials were reviewed by FDA.

VIII. Dosing, Regimen, and Administration Issues

The proposed dose of enfuvirtide is 90 mg twice daily administered by subcutaneous injection. As discussed in Section III of this review, early studies of enfuvirtide showed a dose response relationship: subjects receiving the proposed dose had greater

decreases in plasma HIV RNA. The efficacy of enfuvirtide was clearly evident in Phase 3 clinical trials, which used the proposed dose of 90 mg BID.

The results of study T20-208 suggested that ISRs were more severe in subjects receiving higher doses. Subjects in Phase 3 clinical trials were not allowed to modify their dose of enfuvirtide accordingly; there is no information on the long term consequences of lowering the enfuvirtide dose. Therefore, dose modification is not recommended.

IX. Use in Special Populations

A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation

The overwhelming majority of study participants in the Phase 3 trials were male (90%) and white (89%). The mean age of study participants was 42 years. Two pediatric trials enrolled 39 subjects from three to 16 years of age.

B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy

1. Age

Only four subjects in the Phase 3 clinical studies were older than 65 years of age, so there is very little information about the safety, efficacy and pharmacokinetics of enfuvirtide in the elderly. When the data from T20-301 and T20-302 were analyzed for subjects younger than 40 years compared to 40 years of older, there was no difference in the efficacy or safety results.

2. Gender

Ten percent of subjects (n=102) in Phase 3 clinical trials were female. Population pharmacokinetics from these trials, as well as pharmacokinetic results from other studies, indicate that the clearance of enfuvirtide is 20% lower in females than males after adjusting for body weight.

The treatment effect of enfuvirtide (-1.172 $\log_{10}$ copies/ml) was greater than that of the active control (-1.045 $\log_{10}$ copies/ml) for females but did not reach statistical significance. 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, -1.617 and -1.574 $\log_{10}$

respectively. The lack of statistical significance may relate to the small number of females enrolled in these trials or to the greater treatment response in females in the OB group. The reason for the greater treatment response in females on the OB arm is unclear. However, the absolute effect size of the enfuvirtide + OB arm (-0.572 $\log_{10}$) was similar to that seen in other subgroups. In addition, a greater proportion of women receiving enfuvirtide had plasma HIV RNA levels less than 50 copies/ml (25% vs. 12%), less than 400 copies/ml (37% vs. 30%), and a one log or greater decrease in viral load (48.5% vs. 32%) at week 24. There was also an higher increase in CD4 count from baseline to week 24 in females receiving enfuvirtide.

There was no difference in adverse events, including injection site reactions, between males and females.

3. Race

The majority of subjects in Phase 3 clinical trials were white (89%). Population pharmacokinetics and clinical pharmacology studies indicated that the clearance of enfuvirtide was comparable in blacks and whites but lower in Asian / Pacific Islanders. When clearance is adjusted based on a subject's body weight, there does not appear to be a difference between enfuvirtide clearance in White and Asian subjects.

Because only 10% of subjects in the Phase 3 clinical trials were non-white, efficacy analyses were not performed for individual ethnic minorities. When the treatment effect was analyzed for whites compared to non-whites there was a statistically significant treatment benefit for all non-white subjects receiving enfuvirtide + OB compared to OB alone, similar to the effect seen in white subjects.

There was no difference in adverse events, including injection site reactions, in non-whites.

C. Evaluation of Pediatric Program

Studies T20-204 and T20-310 enrolled 39 HIV-infected pediatric subjects from 3 to 16 years of age. Both studies were single arm, open-label pharmacokinetic and safety studies. All subjects in study T20-204 received 48 weeks of enfuvirtide; study T20-310 is ongoing.

Pediatric subjects were treated with 60 mg/m2/dose of enfuvirtide in T20-204, and with 2 mg/kg/dose in study T20-310. Although pharmacokinetic data in pediatric subjects were more variable than in adult subjects, the exposures for the children in both studies were generally comparable to each other and to adults. Pharmacokinetic data were only available for five children less than six years of age. Due to the interpatient variability and the small number of subjects younger than six years of age, there was insufficient information to make dosing recommendations for children less than six years old.

Although these were small, uncontrolled studies, decreases in HIV RNA were observed in both studies. Six of 14 pediatric subjects in study T20-204 had a log or greater decrease in HIV RNA at week 48. Statistically significant increases in CD4 counts were also reported. Fourteen of 25 children in T20-310 had a one log or greater decrease in HIV-1 RNA at Week 2.

No new safety signals or increased incidence of any specific adverse event were noted in the pediatric clinical trials. Safety appears to be similar to that observed in adults.

Enfuvirtide 2 mg/kg/dose BID will be labeled for the treatment of HIV infection in children six years of age and older.

D. Comments on Data Available or Needed in Other Populations

Additional pharmacokinetic and safety data is needed for children younger than 6 years of age.

There is no data on enfuvirtide in pregnancy or the neonate. There may be a need for enfuvirtide in pregnant HIV-infected women or her neonate if the woman is infected with resistant virus.

There is little available data on HIV-infected subjects older than 65 years of age.

Formal studies were not conducted to assess the effect of renal or hepatic function on enfuvirtide clearance. The applicant partially addressed the effect of hepatic and renal impairment on enfuvirtide exposure in the population pharmacokinetic analyses. The applicant's analyses did not show any relationship between enfuvirtide clearance and the markers of hepatic function (assessed independently) or degree of renal function (> 35 mL/min). In a future submission, the applicant will provide information on the effect of hepatic impairment (based on Child Pugh scores) on enfuvirtide exposure. The applicant will be asked to address the effect of Cl_{cr} < 35 mL/min on enfuvirtide clearance as part of the Phase 4 commitments.

X. Conclusions and Recommendations

A. Conclusions

The treatment of HIV infection with a combination of antiretroviral drugs from two or three different classes has resulted in decreases in both morbidity and mortality. 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.

Enfuvirtide inhibits the fusion of HIV to CD4 positive cells, thereby blocking entry into the cell. It is the first fusion or entry inhibitor to have data submitted for approval in the United States. It is active against HIV-1 that is resistant to the currently approved antiretroviral drugs and offers a new drug for treatment experienced patients with limited treatment options.

The efficacy of enfuvirtide was clearly demonstrated in Phase 3 clinical trials. Subjects who received enfuvirtide plus an optimized background antiretroviral regimen had a statistically significant decrease in plasma HIV RNA from baseline to week 24 compared to those who received the background regimen alone. The treatment effect was also seen in all sensitivity analyses and in subgroup analyses.

There are significant safety concerns with enfuvirtide. Almost all subjects receiving enfuvirtide have injection site reactions, which may be painful and quite large. Despite these reactions, few subjects discontinued enfuvirtide because of injection site reactions, and serious complications of ISRs were rare. Allergic reactions and hypersensitivity reactions were reported in less than 1% of subjects receiving enfuvirtide, and in a few subjects symptoms recurred on rechallenge. None of these reactions were fatal. Finally, there was an increased incidence of bacterial pneumonia in subjects treated with enfuvirtide in the Phase 3 clinical trials. The reason for this was unclear.

Patients treated with enfuvirtide will require extensive education regarding the proper administration of enfuvirtide and the toxicities associated with its use. The applicant has developed multiple materials for patient education, and information regarding the proper use of enfuvirtide and its risks are included in the package insert and patient package insert.

B. Recommendations

Enfuvirtide should be approved for the treatment of HIV-infected patients in treatment experienced adults with evidence of ongoing viral replication. The magnitude of the antiviral effect observed in the Phase 3 trials warrants approval of enfuvirtide. Although there are significant safety concerns regarding enfuvirtide, particularly injection site reactions, hypersensitivity reactions, and the increased risk of bacterial pneumonia, the potential benefit from enfuvirtide use outweighs the known safety concerns. A strong risk management program must be in place on approval to ensure that potential safety hazards associated with enfuvirtide use are minimized. The applicant has developed extensive patient and professional educational materials to address the challenges faced by enfuvirtide use in conditions less controlled than clinical trials. These materials

will significantly enhance patient safety and permit the drug to be used safely in the targeted population.

XI. Appendix

Individual More Detailed Study Reviews

I. Phase 3 Clinical Trials Supporting the Safety and Efficacy of enfuvirtide

A. Study T20-301

Study Design

Phase:	3
Design:	Open-label, randomized, active control
Population:	HIV-infected persons 16 years of age and older
Sites:	International: 48 centers in the United States, Canada, Mexico, and Brazil. Each center could enroll a maximum of 12 patients
Entry Criteria:	(1) Previous experience with ARV therapy from all three antiretroviral classes, defined as treatment with one nucleoside reverse transcriptase inhibitor, one non-nucleoside reverse transcriptase inhibitor, and two protease inhibitors for six months *or* documented resistance to members of each antiretroviral class, (2) maintenance on a stable antiretroviral regimen for at least 4 weeks prior to randomization, and (3) an HIV RNA level of 5,000 copies/ml or greater that was not decreasing.
Study Arms:	Subjects were randomized in a 2:1 ratio to receive enfuvirtide plus an optimized background (OB) antiretroviral regimen or an OB regimen alone. OB was chosen by the physician and the patient based on the patient's treatment history and results of genotypic and phenotypic resistance testing obtained during study screening. The OB regimen could contain three to five drugs and up to two drugs (tenofovir and lopinavir/ritonavir) which were newly approved or investigational at the time of study onset. The optimized background regimen was chosen prior to randomization and 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).
Enfuvirtide Dose:	90 mg administered subcutaneously twice daily
Monitoring:	Weeks 1, 2, 4, 8, 10, 12, 14, 16, 20, 24, 32, 40, and 48.
Efficacy Endpoints	*Primary:* (1) Change in HIV RNA at week 24 (2) Virologic failure at 48 weeks. *Secondary:* (1) Change in CD4 count (2) Incidence of AIDS defining events (3) Death (4) Quality of life survey results (5) Virological response

Safety Analyses: (1) Injection site reactions
(2) Other adverse events

Virological Analyses: Viral sensitivity at baseline, at virologic failure, and at week 48.

Pharmacokinetics: Plasma concentration of enfuvirtide measured during weeks 1 or 2, week 8, week 24, and week 48

Comment: The study inclusion/exclusion criteria appear appropriate for a 'salvage' study, i.e., a study where participants have limited options available. The sponsor has attempted to maximize both the enfuvirtide and 'optimized background' arms by choosing regimens based on phenotypic and genotypic analyses. Although the study is an effective and ethical design for demonstrating that enfuvirtide has activity, it cannot address the exact role of enfuvirtide in early therapy as no direct comparison to any agent commonly used in treatment-naive subjects is possible.

Study Conduct:

Design: Subjects were randomized to either receive OB plus enfuvirtide or OB alone. Subjects receiving OB alone who met the protocol defined criteria for virologic failure could switch to enfuvirtide plus OB after 8 weeks. Subjects receiving enfuvirtide plus OB who met the criteria for virologic failure could continue enfuvirtide plus OB if the physician and subject felt that there was benefit to the subject.

Physicians and subjects who had virologic failure on enfuvirtide were specifically 'encouraged' (as per the protocol) to change the OB component of the regimen after virologic failure, and subjects could receive more than five antiretroviral drugs and immunomodulators after virologic failure. (The protocol specified the OB regimen should contain 3-5 drugs.) Virologic failure was defined as a (1) less than a 0.5 log drop in plasma HIV RNA from baseline on two or three consecutive measurements obtained at least 14 days apart starting at week six , (2) a less than one log decrease in HIV RNA on two or three consecutive measurements obtained at least 14 days apart starting at week 14, or (3) a rebound in plasma HIV RNA levels after initial response (initial decrease of more than two logs documented on two occasions after week 6 followed by an increase in HIV RNA by more than one log). After 48 weeks any subject remaining on the OB arm could add enfuvirtide and subjects on enfuvirtide plus OB could remain on study drugs for an additional 48 weeks.

Virological/immunological analyses: One of the co-primary efficacy endpoints was change in HIV RNA from baseline to week 24. According to protocol defined criteria, a treatment benefit with enfuvirtide would exist if the change in HIV RNA from baseline to week 24 was at least 0.5 $\log_{10}$ copies/ml greater in subjects receiving enfuvirtide plus OB than OB alone. The secondary co-primary endpoint, treatment effect at 48 weeks, was assessed by several interdependent measures, including (1) the proportion of subjects with HIV RNA levels < 50 copies/ml, 50 - 400 copies/ml, and > 400 copies/ml

but with a more than one log decrease in viral load, (2) by the proportion who maintained their 24 week response at week 48, and (3) by the proportion of subjects with virologic failure.

Testing for resistance to enfuvirtide was performed at baseline, at the time virologic failure was detected, and at week 48. Antibodies to gp41 were measured at baseline and at weeks 8, 24, and 48.

Safety Monitoring: Adverse events were recorded at each study visit. Injection site reactions were assessed separately from other adverse events based on results from phase 2 studies indicating this was likely to be the most common adverse event associated with enfuvirtide use. An overall score for injection site reactions was developed based on grades of pain and discomfort; treatment was interrupted for all subjects with Grade 3 injection site reactions and was discontinued for subjects with Grade 4 injection site reactions. Individual signs and symptoms of injection site reactions (erythema, induration, pruritis, nodules, cysts, and ecchymosis) separate from pain and discomfort were also graded.

Tolerability was assessed as the percentage of subjects discontinuing due to adverse events and by the number of injection site reactions.

Pharmacokinetic Sampling: Pharmacokinetic sampling was obtained for subjects receiving enfuvirtide at four times between weeks 1 and week 48. Full profiles were not obtained at any time, but 1-2 samples were targeted for specific time intervals relative to dosing at weeks 1-2, week 8, week 24, and week 48. Please see Dr. Robert Kumi's review for a complete analysis of the clinical pharmacology of enfuvirtide.

Statistical Analysis:

Populations: The primary population for efficacy analysis was the intent to treat population which included all randomized subjects who received at least one dose of study drug and who had a least one post treatment HIV RNA measurement. Efficacy analysis was also performed for a restricted population which excluded subjects who were treated for less than one week, had a major protocol violation, or had less than 85% adherence. The safety analysis population included all patients with at least one follow-up assessment.

Methods: The primary efficacy endpoint was the change in plasma HIV RNA level at 24 weeks. The last value was carried forward for all subjects who discontinued the study or reached the virologic failure endpoint. Analyses were also performed with dropouts classified as nonresponders or with dropouts censored. Secondary efficacy endpoints included change in viral load from baseline to week 8, virologic response at weeks 8 and 24 (HIV RNA< 50 copies/ml, <400 copies/ml, or $\geq$1.0 $\log_{10}$ decrease from baseline), time to virologic response, time to virologic failure, change from baseline CD4 count,

percentage of patients with an AIDS defining illness or death by week 24, and change from baseline to week 24 in Karnofsky score.

Results:

Study Population:

A total of 501 subjects were randomized, 332 to enfuvirtide plus optimized background and 169 to optimized background alone. Baseline characteristics of subjects in both treatment groups are shown in Table 9 below.

Table 9: Baseline Characteristics of Subjects in Study T20-301

	Enfuvirtide plus OB (n= 332)	OB (n = 169)
Ethnicity: Caucasian	84%	82%
Sex: Male	92%	92%
Age (mean)	42	42
Weight (kg)	75.6	76.5
Body mass Index (kg/m^2)	24	24
Mean baseline viral load (log_{10} copies/ml)	5.1	5.1
Mean CD4 count ($cells/mm^3$)	121.3	108.9
Previous AIDS-defining events	83.7%	89.7%

Source: CSR submitted July 16, 2002, Volume 73, page 72, Table 17.

Comment: As shown in the table, baseline viral load, CD4 count, and the percentage of subjects with a previously occurring AIDS defining event were similar in both treatment groups. Most of the study subjects were white males. There were few females and individual ethnic minorities in the study; this substantially reduces the power for demonstrating treatment effects in these subgroups. However, as discussed below, there was a greater treatment response in females and in non-whites in the enfuvirtide + OB arm than in the OB arm.

The mean number of previously received antiretroviral drugs, previous length of treatment with antiretroviral drugs, number of mutations to drugs in each antiretroviral class, genotypic sensitivity score (GSS), and phenotypic sensitivity score (PSS) are shown in Table 10 below.

Table 10: Previous Antiretroviral Treatment Experience

	Enfuvirtide + OB	OB
Mean number of previous antiretroviral drugs	12.3	11.9
Mean duration of previous antiretroviral treatment (years)	7.1	7.3
NRTI mutations (percent of subjects)	91.4%	91.4%
NNRTI mutations (percent of subjects)	83.3%	85.9%
PI mutations (percent of subjects)	83.3%	86.5%
GSS Score : 0	16.0%	13.3%
1-2	51.8%	56.4%
3-4	27.6%	27.3%
≥ 5	4.0%	1.8%
PSS Score : 0	27.6%	24.2%
1-2	42.0%	43.6%
3-4	24.5%	26.7%
≥ 5	4.6%	3.6%

Source: CSR submitted July 16, 2002, volume 73, Pages 72-74, Tables 17, 18

* GSS – measurement of number of antiretroviral drugs to which subject's viral isolate was sensitive or resistant by a genotypic resistance assay (score for each drug tested was 0 for decreased sensitivity and 1 for sensitivity).

**PSS – measurement of number of antiretroviral drugs to which a subject's viral isolate was sensitive or resistant in a phenotypic resistance assay (score for each drug tested was 0 for decreased sensitivity and 1 for sensitivity).

Comment: As shown in Table 10, subjects in study T20-301 had previously received 12 antiretroviral drugs on average and had been treated with antiretroviral drugs for an average of 7 years. Resistance to currently approved antiretroviral drugs was common. This was a difficult population to study because of their advanced disease at baseline (mean CD4 count at baseline < 100 cells/mm^3) and resistance to existing antiretroviral drugs. However, FDA has encouraged sponsors to study this population because of their need for new antiretroviral drugs.

Subject Disposition

Five hundred and one subjects were randomized. Subject disposition is summarized in table 11:

Table 11: Premature Study Discontinuations in Study T20-301

	Enfuvirtide + OB (n = 46)	OB (n = 22)
Discontinued prior to receiving study drug	4	2
Premature Discontinuation	41	22
Injection site reactions	9	n/a
Difficulty w/ injections	4	n/a
Adverse events	15	11
Insufficient treatment response	4	2
Refused Treatment	6	5
Loss to Follow-up	1	3
Incarceration	1	0
Inability to obtain OB drugs	1	0

Source: Exit datasets from July 16, 2002 submission.

Reasons for discontinuation during the first four weeks of treatment with enfuvirtide included injection site reactions (n = 3), problems with injection (2), allergic reaction (2), treatment refusal (1), and adverse events in one subject each (diarrhea, abdominal cramping and bloating, rash, pancreatitis, and pancytopenia).

The most common reasons for study discontinuation for subjects receiving enfuvirtide were adverse events including injection site reactions.

> Comment: The low rate or premature study discontinuation in light of the study population and the low loss to follow-up support a well conducted study with appropriate subject education.

Since enfuvirtide requires twice daily self-administration and frequently results in injection site reactions, the small number of discontinuations due to injection site reactions is striking. Only a few subjects were lost to follow-up or lost due to administrative reasons indicating that the study was conducted properly

The primary study population for determination of efficacy was the intent to treat population. The restricted population, which included subjects with at least 85% compliance with study drug and without major protocol violations, was used as a secondary population in the efficacy analysis. Six subjects in the enfuvirtide + OB arm and four in the OB arm were excluded from the intent to treat population. These subjects were excluded due to lack of post-treatment HIV RNA measurements (two in the enfuvirtide + OB group and two in the OB group), or because they never received study drug (four in the enfuvirtide + OB arm and two in the OB arm). Fifty-six subjects (17%) in the enfuvirtide + OB arm and 25 (15%) in the OB arm were excluded from the restricted treated population. The reasons for exclusion from this population are shown in Table 12.

Table 12: Reasons for Subject Exclusion from the Restricted Treated Population

	Enfuvirtide + OB (n=56)	OB (n=25)
<85% compliance with study drugs	39	16
<3 or >5 drugs in OB regimen	4	0
Changed OB regimen with 2 wks of treatment	13	8
>1 log10 decrease in HIV RNA between screen 1 and 2	1	0
No post-treatment HIV RNA	2	2
Not on stable regimen for ≥4 wks prior to screen 1	0	1
Did not receive treatment	4	2

Source: CSR submitted July 16, 2002, volume 73, Tables 14.

Of the 332 subjects randomized to enfuvirtide + OB arm and 169 randomized to the OB alone arm, 6 subjects in the enfuvirtide + OB arm and 4 in the OB arm were not included in the safety analysis. Two in each group were excluded because lack of follow-up, and the remaining subjects never received study drug.

> Comment: Few study subjects were excluded from either the intent to treat population or the safety analysis. A greater number of subjects were excluded from the restricted population; however, the percentage of subjects excluded was similar in both treatment groups, and the reasons for exclusion were also similar between the two groups. The most common reason for exclusion was less than 85% compliance with the study drug regimen (39 [12%] in the enfuvirtide + OB arm and 16 [9.5%] in the OB group) as measured by a questionnaire administered at week 24. Compliance with antiretroviral drugs is difficult for many reasons including toxicity, food requirements, pill burden, and long term need for treatment. Compliance with enfuvirtide over long periods of time will be challenging for patients because of the need for subcutaneous injection.

Applicant's Analysis of Efficacy

Please see Dr. Hammerstrom's review for the FDA analysis of efficacy.

The primary efficacy endpoint for study T20-301 was the change in plasma HIV RNA from baseline to week 24 with the primary study objective to demonstrate that enfuvirtide 90 mg twice daily plus OB would result in a decrease in plasma HIV RNA suppression of at least 0.5 $\log_{10}$ greater than an OB regimen alone. Results for this endpoint were a mean log decrease from baseline to week 24 for subjects in the enfuvirtide + OB treatment group of –1.696 and for subjects in the OB group –0.764; the difference between the two treatment arms was –0.933 ($p<0.0001$).

At study entry, subjects were stratified by baseline plasma HIV RNA and the number of newly available antiretroviral drugs used in the OB regimen (i.e., lopinavir/ritonavir, tenofovir, both or neither). There was at least a 0.5 $\log_{10}$ difference for all four treatment strata. However, as shown in Table 13, the difference between the two arms was not as pronounced for subjects receiving one or both of the newly available antiretroviral drugs (lopinavir/ritonavir and tenofovir). Either the small number of subjects in this stratum or the larger decrease in HIV RNA for OB subjects receiving one or both of these newly available antiretrovirals may have contributed to the difference in treatment effect.

Table 13: Analysis of Change in Plasma HIV RNA level by Strata

Stratum	Treatment Arm (# of subjects)	Change in HIV RNA from baseline	Difference between arms	p value
HIV RNA <40,000; no new agents	Enfuvirtide + OB (16)	-1.675	-1.181	0.0425
	OB (9)	-0.495		
HIV RNA <40,000; new agents	Enfuvirtide + OB (48)	-1.760	-0.500	0.0456
	OB (24)	-1.260		
HIV RNA >40,000; no new agents	Enfuvirtide + OB (50)	-1.558	-1.098	0.0001
	OB (27)	-0.460		
HIV RNA >40,000; new agents	Enfuvirtide + OB (212)	-1.793	-0.906	<0.0001
	OB (105)	-0.887		

Source: CSR submitted July 16, 2002, volume 74, Page 212

Sensitivity analyses: An analysis was performed on the "restricted" population, defined as study subjects without major protocol violations. Seventeen percent of subjects in the enfuvirtide +OB group and 15% in the OB group were excluded from the "restricted" population: reasons included <85% compliance with study drugs as measured by a questionnaire (12% of enfuvirtide + OB group and 9.5% of OB group) and violation of entry criteria (5% of enfuvirtide + OB group and 5.5% of OB group). In the analysis of the primary efficacy endpoint for this population, the enfuvirtide + OB group again had a statistically significant greater response. The treatment difference was also significant after sensitivity analysis with premature discontinuations counted as treatment failures, and similarly significant with both premature discontinuations and virologic failures counted as treatment failures.

Subgroup analyses: Although study T20-301 was not powered to demonstrate a treatment difference between subgroups, analyses of the primary efficacy endpoint was performed for several demographic subgroups. As shown in Table 14, there was a greater decrease in viral load for each subgroup receiving enfuvirtide + OB than for the

group receiving OB alone. However, the treatment effect did not reach statistical significance in females or in non-white subjects. This is most likely due to the small number of subjects in these subgroups; however, treatment effects are seen in each subgroup.

Table 14: Subgroup Analysis of Mean Change from Baseline in HIV RNA at Week 24 in Study T20-301

	Treatment	Number	Change in HIV RNA	Difference between Arms
Gender				
Male	Enfuvirtide + OB	301	-1.742	-0.905
Male	OB	152	-0.837	
Female	Enfuvirtide + OB	25	-1.725	-0.573
Female	OB	13	-1.152	
Race				
White	Enfuvirtide + OB	274	-1.789	-0.962
White	OB	135	-0.827	
Non-White	Enfuvirtide + OB	52	-1.531	-0.596
Non-White	OB	30	-0.935	
Age				
<40 yrs	Enfuvirtide + OB	135	-1.651	-0.729
<40 yrs	OB	66	-0.921	
>40 yrs	Enfuvirtide + OB	191	-1.815	-1.014
>40 yrs	OB	99	-0.801	

Source: CSR submitted July 16, 2002, volume 73, Page 99

Additional analyses of the primary efficacy endpoint were performed for different subpopulations based on baseline characteristics such as viral load, CD4 count, genotypic sensitivity score, phenotypic sensitivity score, and number of newly available antiretroviral drugs used. Subjects in every subgroup receiving enfuvirtide had a greater treatment effect than those in the subgroup receiving OB alone.

> Comment: Although this study was not designed to determine differences between subgroups, in every subgroup subjects receiving enfuvirtide had a greater decrease in plasma HIV RNA than the corresponding OB alone group. This provides further evidence of the overall treatment benefit associated with enfuvirtide and supports its efficacy in different subgroups.

One secondary efficacy endpoint in study T20-301 was change in plasma HIV RNA at week 8. Since subjects could switch from the OB regimen to enfuvirtide plus OB only after week 8, this analysis included all subjects on their original treatment. The change in $\log_{10}$ HIV RNA for subjects in the enfuvirtide + OB arm at week 8 was –1.738 and for subjects in the OB alone arm was –0.904; the difference between the two treatment arms was –0.834 $\log_{10}$ copies ($p<0.0001$). Additional secondary endpoints were virologic response at week 8 and at week 24. Few subjects in either treatment arm had

a plasma HIV RNA level less than 50 copies/ml at week 8, but significantly more subjects in the enfuvirtide + OB group (19.6%) had plasma HIV RNA levels less than 50 copies/ml at week 24 than in the OB group (7.3%). In this analysis of the intent to treat population, subjects who discontinued were counted as failures. Twenty percent of subjects receiving enfuvirtide had HIV RNA levels less than 400 copies/ml at week 8 compared to 10.9% in the OB arm; the treatment effect was also noted at week 24 (37% with HIV RNA less than 400 copies/ml in the enfuvirtide plus OB group versus 16.4% in the OB alone group). Similarly, more subjects in the enfuvirtide + OB group had at least a one log decrease in plasma HIV RNA at both week 8 (63%) and week 24 (52%) than in the OB alone group (36% at week 8 and 29% at week 24). The change in viral load from baseline to week 8 for all treatment strata is shown in the following table:

Table 15: Change in Plasma HIV RNA from Baseline to Week 24 by Treatment Strata

Stratum	Treatment Arm (# of subjects)	Change in HIV RNA from baseline	Difference between arms	p value
HIV RNA <40,000; no new agents	Enfuvirtide + OB (16)	-1.862	-1.280	0.0065
	OB (9)	-0.582		
HIV RNA <40,000; new agents	Enfuvirtide + OB (48)	-1.675	-0.117	0.6012
	OB (24)	-1.558		
HIV RNA >40,000; no new agents	Enfuvirtide + OB (50)	-1.662	-1.104	<0.001
	OB (27)	-0.558		
HIV RNA >40,000; new agents	Enfuvirtide + OB (212)	--1.758	-0.809	<0.001
	OB (105)	--0.948		

Source: CSR submitted July 16, 2002, volume 74, Page 228.

Virologic failure was defined as plasma HIV RNA less than 0.5 $\log_{10}$ decrease from baseline on two consecutive measurements after week 8, plasma HIV RNA less than 1.0 $\log_{10}$ decrease from baseline on two consecutive measurements after week 16, or initial decrease in plasma HIV RNA of 2.0 $\log_{10}$ or greater followed by a 1.0 $\log_{10}$ rebound. The proportion of subjects with virologic failure through week 24 was 41.7% in the enfuvirtide + OB group compared to 64.2% in the OB alone group. The reasons for virologic failure differed between the two treatment arms; most subjects (74% of those with virologic failure) in the OB arm failed to have a significant decrease in viral load by week 8 while both failure to respond to treatment initially (57%) and initial response with rebound (23.5%) were seen in subjects receiving enfuvirtide.

Comment: Virologic failure was more common in subjects receiving OB alone. The most common pattern of virologic failure in the OB arm was lack of virologic

response by week 8, while the most common pattern of virologic failure in the enfuvirtide + OB arm was initial response followed by virologic failure. This pattern of virologic failure likely represents the high incidence of resistance to currently available antiretroviral drugs at baseline. Subjects in the OB arm never responded because of preexisting resistance to antiretroviral drugs that they received in the study. Subjects in the enfuvirtide arm who were infected with multidrug resistance virus initially responded because of the unique mechanism and resistance pattern of enfuvirtide; these subjects then experienced virologic failure after an initial response due to the development of resistance to enfuvirtide. Because of preexisting resistance to currently approved antiretroviral drugs, these subjects had essentially received enfuvirtide monotherapy.

Efficacy appears to be stronger if HIV-infected patients start at least one other effective drug when beginning enfuvirtide in order to prevent functional monotherapy with enfuvirtide. In subjects with a GSS score of 0 (there were no antiretrovirals to which the patient's isolate was sensitive), 25% of enfuvirtide recipients had a one log or greater decrease in viral load from baseline to week 24; 53% of subjects with a GSS score of 1 or 2 had at one log or greater decrease in viral load. If enfuvirtide is the only effective drug in an antiretroviral regimen, patients with persistent viremia are likely to experience limited benefit from the use of enfuvirtide.

The change in CD4 count from baseline to week 24 was also greater for subjects receiving enfuvirtide, as shown in Table 16 below.

Table 16: Change in CD4 Count from Baseline

	Enfuvirtide + OB	OB	diff.	p value
Baseline CD4 Count (cells/mm^3)	121.3	108.9	---	---
CD4 Count at week 8 (cells/mm^3)	+50.8	+34.7	16.1	0.1065
CD4 count at week 24 (cells/mm^3)	+76.2	+32.1	44.1	0.0001

Source: CSR submitted July 16, 2002, volume 73, Page 95

Other efficacy endpoints: Subjects in Study T20-301 were administered the MOS-HIV questionnaire at baseline and at weeks 4, 8, 16, and 24. There was no statistically significant difference between the physical function scores and the mental health scores in the two treatment groups. It is important to note that there was no decrease in quality of life due to daily self-injection of enfuvirtide detected by this tool. Karnofsky performance scores were measured at baseline and at week 24; scores for the two treatment groups were similar at both timepoints.

In summary, the applicant's analysis of study T20-301 clearly showed the efficacy of an antiretroviral regimen containing enfuvirtide. Subjects receiving enfuvirtide plus an

optimized background regimen of antiretroviral drugs clearly had greater virologic (decrease in plasma HIV RNA) and immunologic (increase in CD4 count) responses than subjects receiving optimized background alone. This treatment benefit associated with the use of enfuvirtide was observed in analyses of the primary and secondary endpoints as well as in subgroup and sensitivity analyses. The robust treatment effect observed in this study may not be duplicated in HIV-infected individual with limited treatment options. In these subjects, enfuvirtide may be the only active drug in their antiretroviral regimen and therefore act as functional monotherapy resulting in early treatment failure.

Applicant's analysis of Safety

Exposure to study drug: A total of 328 subjects received at least one dose of enfuvirtide, and 167 received at least one dose of antiretroviral drugs in the optimized background alone arm. Since subjects in the OB arm could switch to enfuvirtide after week 8, drug exposure is similar between the two treatment groups in the first 10 weeks but differs after that point. At 24 weeks, 88.3% of subjects in the enfuvirtide + OB group were still on study compared to 45.5% in the OB alone group. This translated to a total number of patient years of exposure that was 2.5 times higher in the enfuvirtide + OB group (162.75 patient-years) than in the OB group (64.85 patient-years) at 24 weeks. The difference in study drug exposure continued to increase over time and was 3.9 fold higher four months later at the closure of the database for the Safety Update Report. Reasons for the increased drug exposure to enfuvirtide + OB arm compared to OB alone were: 1) 2:1 randomization, 2) OB subjects could switch to enfuvirtide after virologic failure, 3) more subjects in the OB arm experienced virologic failure, and 4) subjects on enfuvirtide with virologic failure could choose to remain on enfuvirtide.

Overall adverse events: The overall incidence of adverse events, regardless of grade, was 95.4% in the enfuvirtide + OB group and 91.5% in the OB alone group. Adverse events noted in at least 10% of subjects in either treatment arm are shown in Table 17.

Table 17: Adverse Events of Any Grade Reported in At Least 10% of Subjects

Adverse Event	Enfuvirtide + OB	OB
Diarrhea	29.4%	40%
Nausea	25.2%	30.9%
Vomiting	10.4%	17.0%
Upper respiratory tract infection	9.2%	10.9%
Fatigue	23.3%	26.7%
Pyrexia	8.9%	12.7%
Headache	12.9%	12.1%
Peripheral neuropathy	12.3%	6.1%
Dizziness	10.4%	6.1%
Dermatitis	8.3%	13.9%
Insomnia	14.4%	10.3%
Depression	9.8%	10.3%

Source: CSR submitted July 16, 2002, volume 73, Page 118

As shown in above, the most commonly reported adverse events were diarrhea, nausea, and fatigue; each of these was more commonly observed in the OB arm. Adverse events reported more frequently in enfuvirtide recipients included headache, peripheral neuropathy, myalgia, folliculitis, decreased appetite, decreased weight, insomnia, anxiety, and anemia; peripheral neuropathy and decreased appetite were the only adverse events with at least a 5% greater incidence in the enfuvirtide + OB arm. When the incidence of adverse events was adjusted for drug exposure, peripheral neuropathy and decreased appetite were still more common in enfuvirtide recipients; the incidence of peripheral neuropathy was 0.25 events/100 patient years in subjects in the enfuvirtide + OB arm compared to 0.15 events/100 patient years in subjects in the OB arm. Although the proportion of subjects with a decrease in appetite was greater in the enfuvirtide + OB arm, the number of subjects with weight loss was similar between the two treatment groups.

Treatment related adverse events: Except for the reporting of serious adverse events, causality of adverse events was assigned to the study drug regimen in its entirety. For serious adverse events, individual investigators attempted to assign causality to individual drugs in the study regimen. Adverse events that were judged to be treatment related by individual investigators were noted in 77.6% of enfuvirtide recipients and in 74.5% of subjects on OB alone. The most common adverse events attributed to study drug(s) in both treatment groups were diarrhea, nausea, and fatigue. Only peripheral neuropathy and decreased appetite were noted at a greater than 5% incidence in the enfuvirtide + OB arm than the OB arm. Again, the proportion of subjects with weight loss was similar between the two treatment groups.

Adverse events associated with study discontinuation: Adverse events leading to study discontinuation were reported in 6.7% of subjects in the enfuvirtide + OB group and in 4.8% of the OB group. The most frequent adverse events leading to study withdrawal were vomiting and nausea in the enfuvirtide + OB group and vomiting, nausea, and diarrhea in the OB group. All other reasons for study discontinuation were reported in two or fewer subjects. Reasons for discontinuation observed in the enfuvirtide group but not the OB group included insomnia, stress, erythematous rash, hypersensitivity, pancytopenia, and Guillain-Barre syndrome. Hypersensitivity reactions, Guillain Barre syndrome, and the incidence of rash with enfuvirtide will be discussed later in this review.

Severe and life threatening adverse events: Most adverse events in both treatment groups were mild or moderate in severity. Thirty-five percent of subjects in the enfuvirtide group and 30% in the OB alone group had severe adverse events. Potentially life-threatening adverse events, including Grade 4 laboratory values, were reported in 14% of enfuvirtide recipients and in 13% of subjects in the OB arm. The most frequently reported severe adverse events in the enfuvirtide + OB group were fatigue, diarrhea, nausea, anemia, and increased serum triglycerides. Life-threatening

adverse events + Grade 4 laboratory abnormalities reported in enfuvirtide + OB recipients included pancreatitis, increased lipase and amylase, increased liver enzymes, increased GGT, increased CPK, anemia, neutropenia, myocardial infarction, hypoglycemia, and lactic acidosis. All life-threatening adverse events except neutropenia were reported in a higher proportion of subjects receiving enfuvirtide + OB than in those receiving OB alone. However, it is important to remember that the incidence as reported by the applicant was not adjusted for drug exposure; after correction for study drug exposure, the incidence of most life threatening events would likely have been greater in the OB group. In addition, no life threatening adverse events were reported in more than 2% of subjects.

Serious adverse events: Serious adverse events, shown in Table 18, were reported in 26% of subjects in the enfuvirtide + OB group compared to 21% of subjects in the OB group.

Table 18: Serious Adverse Events Reported in At Least 1% of Subjects in Study T20-301

Serious Adverse Event	**Enfuvirtide + OB**	**OB**
↑ CPK	4.3%	2.4%
↑ GGT	2.5%	0
↑ amylase	1.2%	0.6%
↑ lipase	1.2%	0.6%
↑ blood glucose	1.2%	1.2%
neutropenia	2.1%	3.0%
anemia	2.1%	0.6%
pancreatitis	2.1%	0.6%
pyrexia	0.6%	1.2%

Source: CSR submitted July 16, 2002, volume 73, Page 125

The only serious adverse events occurring in more than 2% of subjects in the enfuvirtide + OB group were increased CPK, increased GGT, neutropenia, and pancreatitis; neutropenia was also noted in a higher percentage of subjects in the OB arm. Serious adverse events attributed by investigators to a study drug were reported in 8.6% of enfuvirtide + OB recipients and in 6.1% of subjects in the OB group. Drug relatedness is difficult to determine in this study: subjects received a combination of drugs, many of which have significant toxicities associated with their use. Other adverse events, such as anemia, fatigue, and weight loss, are associated with underlying HIV disease. Drug-related serious adverse events noted in more than one subject receiving enfuvirtide + OB included increased amylase, increased lipase, increased GGT, neutropenia, anemia, and pancreatitis. Adverse events attributed to the study drug, which are of interest but which were only reported in one patient, included Guillain-Barre syndrome, glomerulonephritis, renal impairment, hepatic failure, and hypersensitivity reaction.

Collapsed adverse event terms: Pathophysiologically related or similar adverse event terms were identified by the applicant and summarized collectively, e.g., drug hypersensitivity, hypersensitivity, anaphylactic shock, erythema multiforme, Guillain-Barre syndrome, and membranoproliferative glomerulonephritis were all included in the collapsed term of hypersensitivity reaction. The frequencies of the aggregated terms hypersensitivity, peripheral neuropathy, and lipid disorders were higher in the enfuvirtide + OB group than in the OB alone group. Cutaneous hypersensitivity, which included dermatitis, drug eruption, urticaria, vasculitis, and rashes, was more common in the OB group. Pancreatitis was reported in a similar percentage of subjects in both treatment groups. As shown in Table 19, the incidence of hypersensitivity, peripheral neuropathy, lipid disorders, and pancreatitis were higher in the enfuvirtide + OB group after adjustment for patient-years of exposure.

Table 19: Incidence (Events/100 Patient Years) of Selected Collapsed Adverse Event Terms

Event	Enfuvirtide + OB	OB
Hypersensitivity reactions	0.086	0.031
Peripheral neuropathy	0.258	0.154
Pancreatitis	0.068	0.046
Lipid disorders	0.147	0.139

Source: CSR submitted July 16, 2002, volume 73, Table 48.

Although hypersensitivity reactions are uncommon, they clearly occurred more often in subjects in the enfuvirtide + OB arm. Hypersensitivity reactions associated with enfuvirtide will be discussed later in this review. Peripheral neuropathy and pancreatitis are fairly common adverse events observed in HIV-infected subjects. Pancreatitis and peripheral neuropathy have been associated with the use of didanosine and stavudine; however, the proportion of subjects receiving didanosine and stavudine in the two treatment groups was similar. Therefore, subjects receiving enfuvirtide may be at an increased risk of peripheral neuropathy or pancreatitis. Lipid disorders have been reported in subjects with previous protease inhibitor use; all subjects in study T20-301 had previous treatment with at least 2 protease inhibitors. It is not surprising that the incidence of lipid disorder is increased in this study and the incidence was similar in the two treatment groups.

Injection site reactions: Local injection site reactions (ISRs) were the most common adverse event noted in enfuvirtide + OB recipients. ISRs were assessed at each study visit using a standardized tool that graded the overall reaction (defined by the degree of pain and discomfort) as well as individual signs and symptoms. Almost all subjects (98.2%) had an ISR during the first 24 weeks of the study. The large majority of subjects reported an ISR at the first study visit (88%), and ISRs continued to be reported throughout the time on study. The incidence of subjects with an ISR at study visits from week 2 to week 24 ranged from 60% to 74.5%. Most ISRs (96%) were associated with pain or discomfort; 9% of subjects needed narcotics for the pain associated with an ISR. Individual signs and symptoms were commonly reported:

erythema (87%), induration (84%), nodules or cysts (82%), pruritis (64%), and ecchymosis (51.5%). The erythema was often extensive and approximately 30% of subjects had erythema more than 50 mm in diameter. Almost one-half of subjects had Grade 3 or 4 induration (≥ 25 mm). Approximately 25% of subjects had nodules or cysts that were greater than or equal to 30 mm in size. Pruritis and ecchymosis were usually mild (85% with Grade 1 pruritis and 87% with Grade 1 or 2 ecchymosis). Most subjects had one to five lesions at any point in time. Individual lesions usually lasted less than 7 days. The severity of ISRs and of individual signs and symptoms did not appear to increase over time. In addition, although ISRs were common and were associated with multiple signs and symptoms, only 3% of subjects discontinued the study because of ISRs.

Deaths: There were four deaths in the enfuvirtide + OB group, four in the OB alone group, and one in a patient after switching from OB to a enfuvirtide containing regimen. The four deaths in the enfuvirtide + OB arm were due to Guillain-Barre syndrome, pancreatitis, and sepsis (2). The four deaths in the OB alone arm were due to AIDS encephalopathy, progressive HIV infection, lymphoma, and toxoplasmosis. The one death in a switch subject was due to sepsis. Deaths in subjects receiving enfuvirtide are described below.

1) Subject 1043 was a 46 year old male receiving enfuvirtide plus zidovudine, zalcitabine, efavirenz, and nelfinavir. He was admitted on study day 159 with an elevated white blood cell count and a two day history of increasing abdominal pain. At laporotomy, he was diagnosed with a perforated colon and a colectomy with terminal colostomy was performed. He developed septic shock 16 hours post-operatively and died of cardiac arrest on day 161.

2) Subject 1503 was a 58 year old male with a history of peripheral neuropathy, oral candidiasis, and pneumocystis pneumonia. On day 27 he was hospitalized with a seven day history of difficulty initiating urinary flow, problems swallowing, and a two day history of bilateral lower extremity weakness with falling. After a lumbar puncture, he was diagnosed with Guillain Barre syndrome and plasmapheresis was started. On day 38, he aspirated food, developed left lower lobe pneumonia, and required intubation. On day 39, he extubated himself and declined further treatment. The subject died of respiratory failure on day 40.

3) Subject 1771 was a 42 year old male with a history of chronic renal insufficiency, hepatitis, PCP, and oral candidiasis who was randomized to enfuvirtide + OB. On day 111 he presented with fever to 101.9°F and a three day history of vomiting. Admission laboratory values included serum creatinine of 10 mg/dL and serum potassium of 7.2 meq/dL. The subject was started on dialysis. His admission blood and urine cultures were positive for E.coli, so he was started on antibiotics. On day 117, he developed disseminated intravascular coagulopathy and suffered cardiac arrest. He died on day 118.