4) Subject 1904 was a 38 year old male with a history of PCP and CMV retinitis. He was randomized to enfuvirtide and also began lopinavir/ritonavir and stavudine. The subject was treated with intravenous pentamidine from days 15 to 23. On day 24, he was hospitalized with pancreatitis (amylase=339 U/L, lipase=1089 U/L). On day 27, enfuvirtide was stopped. The subject died on day 27; pancreatitis was listed as his cause of death.

5) Subject 1428 was a 47 year old male with a history of non-Hodgkins lymphoma and neutropenia. His treatment course before and after switch to enfuvirtide was complicated by neutropenia requiring treatment with filgastrim. On day 122 after switching to enfuvirtide, he was hospitalized with left lower lobe pneumonia and neutropenia. Blood cultures were positive for *Staphylococcus aureus* and *Pseudomonas* species. His hospital course was complicated by myocardial infarction, renal failure, and cerebrovascular accident. On day 191, he stopped all antiretroviral drugs including enfuvirtide. He died on day 193. The cause of death was listed as sepsis and advanced AIDS.

> Comment: The only death judged by an investigator to be treatment related was the death due to Guillain Barre syndrome. Since most HIV-infected subjects have antibodies to gp41, there is concern that antibody-enfuvirtide complexes could be formed in subjects on enfuvirtide and that this may result in a higher incidence of immune complex disease such as Guillain Barre syndrome. This possible pathogenesis cannot be ruled out in this study subject. However, the incidence of possible immune complex mediated adverse events were rare in this study. Despite this, healthcare providers and patients must be informed about the risk of developing diseases due to immune complex formation.

Laboratory adverse events: Laboratory values were analyzed for mean and median change from baseline to week 24 and for proportion of subjects with new Grade 3 and Grade 4 laboratory abnormalities. Laboratory values that changed over time with a greater magnitude of change in the enfuvirtide + OB group included increases in BUN, calcium, HDL, and cholesterol and decreases in ALT, AST, GGT, and albumin. Increases in CPK, lipase, and LDL were also noted in enfuvirtide recipients.

New Grade 3 abnormalities reported in at least 5% of subjects receiving enfuvirtide included increases in triglycerides, CPK, amylase, and lipase. The most commonly reported Grade 3 laboratory abnormality was an increase in triglyceride levels, which was reported in 12% of enfuvirtide + OB subjects and in 10% of OB subjects. Grade 4 laboratory abnormalities were observed in 13% of subjects receiving enfuvirtide + OB compared to 10% of subjects receiving OB. The most commonly reported Grade 4 abnormalities in enfuvirtide recipients were increases in CPK (4.3%) and GGT (4.3%). Other Grade 4 laboratory abnormalities observed in at least 2% of subjects receiving enfuvirtide were neutropenia (2.5%) and increased lipase (2.1%).

As mentioned earlier in this review, lipid abnormalities are commonly observed in HIV-infected subjects with advanced disease and exposure to protease inhibitors. Increases in amylase and lipase are consistent with the increase in pancreatitis noted in enfuvirtide recipients after analysis of collapsed adverse event terms. It is unclear why there was an increased incidence of increased CPK in the enfuvirtide + OB arm. Differences observed between the two treatment arms may change with adjustment for exposure to study drug, however this information was not provided by the applicant.

Switch subjects: In study T20-301 subjects originally randomized to the OB arm with virologic failure could switch to a enfuvirtide containing regimen any time after week 8. These subjects continued to be followed on study. Eighty-one subjects originally randomized to the OB regimen switched to a enfuvirtide containing regimen after experiencing virologic failure. Data for these subjects, including adverse event information, were available for up to 16 weeks after switching to enfuvirtide.

Adverse events were reported in 78% of switch subjects; the most commonly reported adverse events were diarrhea, fatigue, and nausea. Adverse events of severe intensity were reported in 14% of switch subjects, with only renal calculus occurring in more than one subject. Life threatening adverse events were reported in 5% of switch subjects. Grade 4 neutropenia was observed in six subjects and Grade 4 increases in lipase was reported in two subjects. Serious adverse events were reported in 12% of switch subjects; four of these were treatment related as judged by the individual investigator (increased GGT, neutropenia, renal stone, hydronephrosis). Three switch subjects discontinued the study early – one due to diarrhea, one due to advanced HIV disease, and one due to ISRs. Injection site reactions were common in the switch group (96%) and signs and symptoms were similar to those reported in subjects initially randomized to enfuvirtide + OB. Finally, there was one death in the switch group due to sepsis. This subject was a 47 year old male with a history of non-Hodgkins lymphoma and neutropenia whose treatment course on enfuvirtide was complicated by neutropenia. On day 122 after switching to enfuvirtide, he was hospitalized with left lower lobe pneumonia, neutropenia; and bacteremia. His hospital course was complicated by myocardial infarction, renal failure, and a cerebrovascular accident. On day 191, he stopped all antiretroviral drugs including enfuvirtide. He died on day 193. The cause of death was listed as sepsis and advanced AIDS.

In summary, the applicant concluded that enfuvirtide was well tolerated in study T20-301. Injection site reactions were the most common adverse event seen in subjects receiving enfuvirtide. ISRs occurred in almost all patients and recurred throughout the study; subjects with ISRs reported multiple signs and symptoms such as pain, induration, erythema, and cysts and nodules. The incidence of certain adverse events such as hypersensitivity reactions, pancreatitis, and peripheral neuropathy, were more common in enfuvirtide recipients. However, most adverse events were seen in a similar proportion of subjects in both treatment groups and were consistent with advanced HIV disease and toxicity from other antiretroviral drugs.

B. Study T20-302

Study Design

Like study T20-301, study T20-302 was a Phase 3, open-label, randomized, active control study of the safety and efficacy of enfuvirtide plus an optimized background regimen compared to an optimized background regimen alone in HIV-infected, treatment-experienced subjects. The study protocols for Study T20-301 and T20-302 were identical except for slight differences in the inclusion criteria; 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. See pages 55-56 for a detailed description of the study design of T20-301.

Results

Study Population

A total of 512 subjects were enrolled in T20-302; 341 were randomized to receive enfuvirtide plus an optimized background regimen and 171 to receive the optimized background regimen alone. Baseline characteristics of subjects in both treatment groups are shown in Table 20 below.

Table 20: Baseline Characteristics of Subjects in Study T20-301

	Enfuvirtide + OB	OB
Ethnicity: Caucasian	94%	95%
Sex: Male	87%	88%
Age (mean)	42	43
Weight (kg)	69	69
Body mass index	22	22
Mean baseline viral load (log_{10} copies/ml)	5.1	5.1
Mean CD4 count (cells/mm^3)	150.6	146.2
Previous AIDS-defining events	74.6%	81.7%

Source: CSR submitted July 16, 2002, Volume 182, page 71.

Comment: The study population in study T20-302 was similar to that of study T20-301. As shown in Table 20, baseline viral load, CD4 count, and percentage of subjects with a previously diagnosed AIDS defining event were similar in both treatment groups. Most of the study population had advanced HIV disease as evidenced by the high viral load, the low CD4 count, and the high proportion with a previous AIDS defining event at baseline. Most of the study population was male and Caucasian. As in study T20-301, although there were too few females and individual ethnic minorities to determine a statistically significant treatment

benefit, a greater treatment response was observed for females and non-whites in the enfuvirtide + OB arm than in the OB arm.

The mean number of previous antiretroviral drugs was 12 in each treatment group, and subjects had previously received antiretroviral drugs for a mean of seven years in both groups. The number of mutations to drugs in each antiretroviral class, the genotypic sensitivity score, and the phenotypic sensitivity score were also similar between the two groups.

Comment: This was a heavily pretreated study population and resistance to currently approved antiretroviral drugs was common at baseline. This study population is representative of HIV-infected patients who are treatment experienced, have advanced disease, and are in need new antiretroviral drugs with unique resistance patterns.

Subject Disposition

Study T20-302 was conducted by investigators at 67 sites in Western Europe and Australia. The first subject was enrolled in February 2001 and the last subject completed 24 weeks of treatment in January 2002. A total of 512 subjects were enrolled in T20-302; 341 were randomized to receive enfuvirtide plus an optimized background regimen and 171 to received the optimized background regimen alone. Three subjects in the enfuvirtide + OB group and one in the OB group discontinued the study before receiving study drug. Of the 338 subjects who received at least one dose of enfuvirtide, 60 subjects prematurely discontinued the study including one subject who was lost to follow-up before any safety or efficacy information was obtained and two who discontinued with any post-treatment efficacy data obtained. Of the 170 subjects who received at least one dose of the OB regimen, seven discontinued the study prematurely including one patient without follow-up and 114 who switched to a enfuvirtide containing regimen after virologic failure on an optimized background regimen. Nine subjects withdrew from the study after switching to enfuvirtide from the OB arm. Therefore, 337 subjects in the enfuvirtide + OB arm were included in the safety analysis and 335 in the intent-to-treat analysis of efficacy; there were 169 OB subjects in both the safety and ITT populations for analyses.

A total of 57 (17%) subjects in the enfuvirtide + OB arm and 17 (5%) in the OB arm discontinued the study before week 24. The primary reason for study withdrawal in the enfuvirtide + OB group was an adverse event. The primary reason for withdrawal in the OB group was virologic failure; 114 subjects in the OB arm switched to a enfuvirtide containing regimen after week 8. Reasons for premature study discontinuation are shown in Table 21 below:

Table 21: Reasons for Premature Study Discontinuation in Study T20-302

Reason	Enfuvirtide + OB (n=335)	OB (n=169)	
		Remained on OB (n=55)	OB after Switch (n=114)
Total	**57**	**8**	**9**
Adverse Event	23	1	3
ISR	11	--	3
Abnormal Lab Value	1	0	0
Death	2	1	1
Insufficient Therapeutic Response	14	4	2
Refused treatment	6	2	0
Other	3	0	0

Source: CSR submitted July 16, 2002, volume 182, Page 68

As shown in Table 21, 34 of 57 subjects receiving enfuvirtide + OB withdrew from study T20-302 due to an adverse event; 11 had injection site reactions and another discontinued because he was tired of injecting enfuvirtide. The second most common adverse event resulting in study discontinuation was depression (6 subjects). Several subjects discontinued because of infectious events (sepsis-2, pneumonia-1); one subject discontinued after a hypersensitivity reaction which was attributed to enfuvirtide, two subjects discontinued after the development of rashes, and one subject developed hepatitis. Adverse events associated with progression of HIV infection were common (PML, lymphoma, Kaposi's sarcoma). The overwhelming majority of subjects in the OB arm either discontinued the OB arm due to virologic failure or stopped treatment because of insufficient therapeutic response (118/169 or 70%). Six subjects from the switch group discontinued due to adverse events: this included three switch subjects with ISRs and two with anxiety related to the ISRs. Deaths will be discussed in Section I.C.8.

The main reason for study discontinuation was injection site reactions, however, only 3% of subjects withdrew for this reason. Another 8% withdrew because of adverse events, abnormal laboratory values, or death. Few subjects discontinued the study due to administrative reasons or loss to follow-up.

Applicant's analysis of Efficacy

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

As in study T20-301, the primary efficacy endpoint in study T20-302 was the change in plasma HIV-1 RNA from baseline to week 24. The change from baseline to week 24 in $\log_{10}$ HIV RNA in the intent to treat population was –1.429 in the enfuvirtide + OB group

and –0.648 in the OB group; the difference between the two treatment arms was –0.781 ($p<0.0001$). Study subjects were stratified at baseline by viral load (<40,000 or ≥40,000 copies/ml) and number of newly available antiretroviral drugs used (lopinavir/ritonavir, tenofovir, neither or both). A statistically significant treatment benefit was observed in all strata.

The treatment benefit was also noted when the analysis was limited to a restricted population. This population included subjects with at least 85% compliance with study drugs and with no major protocol violations; 18% of the subjects in the enfuvirtide + OB arm and 22% of the subjects in the OB arm were excluded from this analysis primarily due to noncompliance (11% in enfuvirtide + OB arm and 14% in OB arm). In this analysis subjects in the enfuvirtide + OB group had a –0.704 greater decrease in $\log_{10}$ HIV RNA level ($p<0.0001$).

Sensitivity analyses: The treatment difference was also statistically significant after sensitivity analyses when premature discontinuations were counted as failures and when both premature discontinuations and virologic failures were counted as treatment failures. Cohort analysis was done to detect treatment differences for subjects who completed treatment on their originally assigned treatment at weeks 4, 8, 12, 16, 20, and 24. There was a statistically significant difference at all but weeks 20 and 24; this is probably because the small number of subjects remaining in the OB arm on subjects at week 20 and 24 had remained on their OB regimen only because of virologic success.

Subgroup analyses: Study T20-302 was not designed to discern treatment differences between subgroups. As shown in Table 22, subjects in all subgroups receiving enfuvirtide had a greater treatment effect than those on OB alone.

Table 22: Subgroup Analysis of Mean Change from Baseline in HIV RNA at Week 24 in Study T20-302

	Treatment	Number	Change in HIV RNA	Difference between Arms
Gender				
Male	enfuvirtide + OB	292	-1.407	-0.757
Male	OB	148	-0.649	
Female	enfuvirtide + OB	43	-1.516	-0.567
Female	OB	21	-0.950	
Race				
White	enfuvirtide + OB	316	-1.403	-0.689
White	OB	161	-0.714	
Non-White	enfuvirtide + OB	19	-1.735	-1.643
Non-White	OB	8	-0.093	

Age				
<40 yrs	enfuvirtide + OB	146	-1.227	-0.386
<40 yrs	OB	60	-0.841	
>40 yrs	enfuvirtide + OB	189	-1.569	-0.964
>40 yrs	OB	109	-0.605	

Source: CSR submitted July 16, 2002, volume 182, Page 98.

The treatment difference was not statistically significant for females or for subjects less than 40 years of age.

> Comment: The lack of statistical significance for females may be related to the small number of women enrolled in the study. However, there was a greater treatment effect for all subjects receiving enfuvirtide, and the study was not powered to detect treatment differences between subgroups.

Subgroup analyses were also performed based on baseline characteristics such as viral load, CD4 count, genotypic and phenotypic sensitivity score, and number of newly available antiretroviral drugs used.

> Comment: Again, the treatment benefit was not always statistically significant, but for each subgroup subjects receiving enfuvirtide plus OB had greater decreases in viral load compared to those receiving OB alone.

Secondary efficacy endpoints: Secondary efficacy endpoints analyzed included change in plasma HIV-1 levels from baseline to week 8. There was a mean decrease in viral level of –1.526 $\log_{10}$ for subjects in the enfuvirtide + OB arm and of –0.812 for those in the OB arm ($p<0.0001$). The applicant also calculated the percentage of subjects with plasma HIV levels less than 50 copies/ml, with less than 400 copies/ml, and with a $\log_{10}$ or greater decrease in viral load at week 24. Few subjects in either group (12% in the enfuvirtide + OB arm and 5% in the OB arm) had viral loads less than 50 copies/ml at week 24. Twenty-eight percent of subjects receiving enfuvirtide plus OB had viral loads less than 400 copies/ml compared to 14% in the OB group. Twice as many subjects in the enfuvirtide + OB arm (43%) as in the OB arm (21%) had a one log10 decrease in HIV-1 viral load.

Virologic failure was more common in the OB group; 49% of subjects in the enfuvirtide + OB group and 77% in the OB group met the criteria for virologic failure at week 24. The type of virologic failure differed between the two treatment groups. Subjects in the enfuvirtide + OB group were more likely to achieve initial viral suppression then experience rebound while subjects in the OB group never experienced a decrease in viral load. There was also a statistically significant increase in CD4 count at week 24 for subjects in the enfuvirtide + OB arm compared to those in the OB arm (+65.5 vs. +38.0 cells/mm^3, $p=0.0236$).

Other efficacy endpoints: Subjects in study T20-302 were administered the MOS-HIV questionnaire at baseline and at weeks 4, 8, 16, and 24. Changes from baseline to week 24 were analyzed for the physical function and mental health scales of this questionnaire. There was evidence of improvement from baseline in both groups. There was no statistically significant difference between the two treatment groups. Karnofsky scores were also followed in study T20-302; changes in Karnofsky scores between baseline and week 24 were not seen in either treatment group.

In summary, in the applicant's analyses of study T20-302, subjects receiving enfuvirtide plus an optimized background regimen had a statistically significant decrease in plasma HIV viral levels from baseline to week 24 compared to those receiving OB alone. A treatment benefit was also noted after sensitivity analysis of the primary endpoint and for all secondary efficacy endpoints. In addition, subjects in all subgroups who received enfuvirtide and an OB regimen had a greater decrease in viral load than those receiving viral load. Finally, immunologic improvement, as measured by the increase in CD4 count, was significantly better in subjects receiving enfuvirtide.

Applicant's analysis of Safety

Exposure to study drug: A total of 508 subjects received at least one dose of study drug and had at least one follow-up visit: 337 in the enfuvirtide + OB group and 169 in the OB alone group. The exposure to study drug from randomization to week 24 differed between the two study groups; the total number of patient years of exposure was 2.7 fold higher for the enfuvirtide + OB group (162.8 patient-years) compared to the OB alone group (60.4 patient-years). This was due to several features of the study designs including the 2:1 randomization, the switch of subjects with virologic failure on the OB arm to a enfuvirtide containing regimen after week 8, and allowance for subjects in the enfuvirtide + OB arm with virologic failure to remain on enfuvirtide. By week 24, 114 (88%) of subjects in the OB arm had experienced virologic failure and switched to a enfuvirtide containing regimen, while 131 subjects in the enfuvirtide + OB arm had experienced virologic failure and decided to remain on enfuvirtide.

Overall adverse events: As would be expected in a treatment experienced patient population with advanced HIV disease, the incidence of adverse events was high in each treatment group: 91% in the enfuvirtide + OB arm and 87% in the OB alone arm. Adverse events reported in at least 10% of either treatment arm are shown in Table 23 below:

Table 23: Adverse Events Reported in At Least 10% of Subjects

Adverse Event	enfuvirtide + OB	OB
Diarrhea	24.3%	27.2%
Nausea	15.1%	16.6%
Pyrexia	10.7%	10.1%
Headache	10.7%	10.1%
Asthenia	10.4%	7.7%

Source: CSR submitted July 16, 2002, volume 182, Page 115.

As shown in Table 23, the most common adverse events reported in study T20-302 were diarrhea and nausea. Adverse events reported in five to 10% of subjects in the enfuvirtide + OB arm included vomiting, fatigue, peripheral neuropathy, dermatitis, and pruritis. Infectious adverse events were common; oral candidiasis was reported in 7.4% of enfuvirtide + OB subjects and 8.3% of OB subjects, bronchitis was reported in 6.2% of enfuvirtide + OB subjects and 7.7% of OB subjects, and herpes simplex was reported in 6.5% of enfuvirtide + OB subjects and 5.3% of OB subjects. Psychiatric adverse events were reported in more subjects in the enfuvirtide + OB group than in the OB group; these adverse events included insomnia (8.3% in the enfuvirtide + OB group vs. 7.1% in the OB group), depression (7.4% in the enfuvirtide + OB group vs. 4.1% in the OB group), and anxiety (5.0% in the enfuvirtide + OB group vs. 1.2% in the OB group). The incidence of these adverse events by patient exposure years was not provided.

Adverse events associated with study discontinuation: Causality of treatment related adverse events was assigned to the entire study drug regimen unless the adverse event was serious; for serious adverse events, investigators attempted to relate causality to individual drugs. Adverse events attributed by an individual investigator to a study drug were reported in 71.5% of subjects in the enfuvirtide + OB arm and 67.5% of subjects in the OB arm. The types of drug related adverse events were similar in the two groups. The most common adverse events attributed to a study drug(s) were diarrhea, nausea, and fatigue. There were no treatment related adverse events with a 5% greater difference in the enfuvirtide + OB arm compared to the OB arm.

Adverse events associated with study discontinuation: Adverse events leading to study discontinuation were reported more commonly in the enfuvirtide + OB group (7.7%) than in the OB group (1.2%). This analysis by the applicant did not include study discontinuations due to injection site reactions. The most common reason for study discontinuation in the enfuvirtide + OB group was depression (6 subjects in the enfuvirtide + OB group vs 0 in the OB group). The only reasons for study withdrawal that were observed in at least two subjects of the enfuvirtide + OB group were vomiting (2 subjects) and hypersensitivity reaction (2 subjects). Reasons for discontinuation reported in the enfuvirtide + OB group but not the OB group included anxiety, pancreatitis, asthenia, fatigue, bacterial pneumonia, sepsis, pancytopenia, thrombocytopenia, hepatitis, increased transaminases, and rash.

Severe and life threatening adverse events: The majority of adverse events were of mild or moderate intensity. Severe adverse events were reported in 31.5% of subjects in the enfuvirtide + OB arm and in 22.5% of subjects in the OB arm. The slightly higher incidence in subjects receiving enfuvirtide was not due to any specific adverse event. The only severe adverse events occurring in more than 1% of subjects in the enfuvirtide + OB arm were pyrexia, asthenia, depression, anxiety, back pain, and increased triglyceride level. Potentially life-threatening adverse events were reported in 7.4% of subjects in the enfuvirtide + OB arm and 5.9% of subjects in the OB arm. Life threatening adverse events included both clinical events and all Grade 4 laboratory abnormalities. Clinical life-threatening adverse events reported in the enfuvirtide + OB arm were bronchopneumonia, suicide attempt, and hepatitis. Laboratory abnormalities reported as life threatening adverse events were increased GGT, increased lipase, and neutropenia. Grade 4 increases in GGT and neutropenia were observed more commonly in the OB group; life threatening pancreatitis and Stevens-Johnson syndrome were reported in the OB group but not the enfuvirtide + OB group.

Serious adverse events: Serious adverse events included all Grade 4 laboratory values and were reported in 23.7% of enfuvirtide + OB recipients compared to 24.3% of the OB group. Serious adverse events reported in at least 1% of subjects are shown in Table 24.

Table 24: Serious Adverse Events Reported in At Least 1% of Subjects in Study T20-302

Serious Adverse Event	**Enfuvirtide + OB**	**OB**
pancreatitis	7 (2.1%)	3 (1.8%)
increased GGT	6 (1.8%)	7 (4.1%)
increased lipase	5 (1.5%)	1 (0.6%)
pneumonia	4 (1.2%)	1 (0.6)
neutropenia	4 (1.2%)	3 (1.8%)
anemia	4 (1.2%)	2 (1.2%)
pyrexia	3 (0.9%)	4 (2.4%)
renal impairment	1 (0.3%)	2 (1.2%)
urinary tract infection	0	2 (1.2%)
increased CPK	0	6 (3.6%)

Source: CSR submitted July 16, 2002, volume 182, Page 123.

Pancreatitis was the only serious adverse event observed in more than 2% of subjects in the enfuvirtide + OB group. Only increased lipase and pneumonia were reported more frequently in the enfuvirtide + OB group than in the OB alone group. Adverse events judged by the investigator to be drug related that were reported in more than one subject in the enfuvirtide + OB group included increased GGT, increased lipase, increased transaminases, pancreatitis, anemia, and hepatitis. Drug related adverse events of interest that were only reported in one subject included injection site abscess and depression.

Collapsed adverse event terms: The applicant identified similar preferred terms for adverse events and collapsed these terms into adverse events of special interest. For example, drug hypersensitivity, hypersensitivity, and Stevens Johnson syndrome were all included in the special collapsed category of hypersensitivity. Hypersensitivity reactions were more common in the OB group. There were eight adverse events labeled as either drug hypersensitivity or hypersensitivity in the enfuvirtide + OB group compared to five in the OB group; there was also one report of Stevens Johnson syndrome in the OB group. However, cutaneous hypersensitivity reactions such as dermatitis, drug eruption, and rash were more common in the enfuvirtide + OB group. The incidence of all types of rash was higher in the enfuvirtide + OB arm (11 episodes of rash and 21 of dermatitis compared to 1 episode of rash and 10 of dermatitis); however, there were two episodes of urticaria in the OB group and none in the enfuvirtide + OB group. Finally, pancreatitis was more common in the enfuvirtide + OB group while lipid disorders and peripheral neuropathies were more common in the OB group.

Injection site reactions: Injection site reactions were the most commonly reported adverse events and occurred in 98% of subjects receiving enfuvirtide. Eighty-three percent of subjects had ISRs during the first week of the study, but ISRs were reported throughout the study. Sixty-five percent or more of subjects had an ISR at any single study visit during the trial. ISRs were graded on separate scales for individual signs and symptoms such as pain, erythema, induration, cysts and nodules, pruritis, and ecchymosis. Signs and symptoms associated with ISRs were extremely common with pain, induration, and erythema reported in more than 90% of subjects. These signs and symptoms could be significant: 10% of subjects required narcotics for pain, 30% had erythema of 50 mm or more, 60% had 25 mm or more of induration, and 29% had nodules or cysts that were 30 mm or more in size. Subjects often had more than one ISR at a time; 76.5% had from one to five lesions present when examined. Individual ISRs usually lasted for less than seven days. The severity of signs and symptoms did not increase over time; similarly the types of signs and symptoms associated with ISRs generally did not change over time on enfuvirtide. One ISR, an abscess, was reported as a serious adverse event. Eleven subjects (3%) discontinued the study because of an ISR; two subjects discontinued the study because of their aversion to injections.

There were six deaths in the enfuvirtide + OB group, one in the switch group, and one in the OB group. The cause of death for subjects receiving enfuvirtide was variable and included pneumonia (2 subjects), cardiac failure, suicide, cytomegalovirus infection, and end stage AIDS. The suicide was considered treatment related; this subject had a history of depression at study entry and developed considerable anxiety due to difficulty with self-injection of enfuvirtide. The one death in the OB group was due to advanced HIV disease. A more complete description of the deaths in enfuvirtide recipients is included below:

1) Subject 6156 was a 45 year old male with a history of depression and anxiety. He was randomized to enfuvirtide and started an OB regimen of tenofovir, efavirenz, and

lopinavir/ritonavir. On day 1 he reported a drunken feeling and increased depression related to difficulties in preparation and injection of enfuvirtide. The subject reported ISRs during the first two weeks that included Grade 3 pain, Grade 3 induration, Grade 2 erythema, and Grade 2 nodules/cysts. At his week 2 study visit, he had more than six ISRs present. The subject visited the study site daily to show the study personnel his ISRs. On day 19, he committed suicide.

2) Subject 5183 was a 38 year old male with a history of bronchiectasis, recurrent pseudomonas chest infection, and recurrent pneumonia was randomized to enfuvirtide plus OB. On day 48 he was hospitalized with an exacerbation of his pseudomonas chest infection that did not resolve on treatment. On day 53 he was diagnosed with lymphoma. The subject discontinued all medications on day 79. He died on day 83; the cause of death was bronchopneumonia.

3) Subject 5184 was a 44 year old male who was hospitalized on day 65 for evaluation of headache, diplopia, and sixth nerve palsy. During the hospitalization, the subject had a generalized tonic clonic seizure and aspirated. The subject died of bronchopneumonia on day 93.

4) Subject 4098 was a 50 year old male with a history of oral candidiasis, CMV, and chronic diarrhea. In spite of continued treatment for CMV, he died of CMV disease on day 115.

5) Subject 7064 was a 61 year old male with a history of CMV, Kaposi's sarcoma, candidiasis, liver necrosis, and two undiagnosed liver lesions. On day 12, the liver lesions were diagnoses as non Hodgkins lymphoma. The subject attempted suicide on day 17. On day 52, he died of myocardial infarction associated with sepsis.

6) Subject 7211 was a 46 year old male with a history of seizures, Kaposi's sarcoma, pancytopenia, hepatitis B infection, and lower extremity pain. The lower extremity pain recurred on several occasions during the study. On day 115, he developed involuntary movements on his lower extremities, and on day 132 the subject complained of lower extremity weakness. The subject was hospitalized for pain control and end stage AIDS on day 168. All medicines were stopped, and the subject died on day 175. Autopsy showed coronary sclerosis, fibrosis of myocardium, bilateral pneumonia, and hepatic steatosis.

7) Subject 1131 was a 47-year-old white male with candidiasis, HIV dementia, wasting, Von Willebrand's disease, congestive heart failure, mitral valve insufficiency, non-rheumatic tricuspid valve insufficiency, pulmonary hypertension, Raynaud's disease, and cardiomyopathy secondary to HIV disease. He was randomized to OB and switched to enfuvirtide on day 106. The subject was hospitalized six days later because of pulmonary edema. All antiretrovirals including enfuvirtide were stopped. The subject died on day 113 due to pulmonary edema associated with his underlying heart disease.

Laboratory adverse events: Adverse events for laboratory parameters were determined by the change from baseline and the number of treatment emergent Grade 3 and Grade 4 abnormalities. Laboratory values in which there was a change from baseline in both treatment groups but with a more pronounced change in the enfuvirtide group included increases in platelet count, white blood cell count, lymphocytes, eosinophils, and bilirubin and decreases in neutrophils. Laboratory parameters with Grade 3 abnormalities reported in 5% or more of subjects receiving enfuvirtide were increases in triglycerides, amylase, and lipase. There were no laboratory values for which at least 5% of subjects had a Grade 4 abnormality. Grade 4 abnormalities noted in at least 2% of subjects receiving enfuvirtide + OB included increases in ALT and lipase. Increases in AST, ALT, GGT were also more common in the enfuvirtide + OB group than in the OB group. In summary, although laboratory abnormalities were not uncommon in subjects in study T20-302, Grade 3 and 4 abnormalities were rarely reported in more than 5% of subjects.

Switch subjects: In study T20-302, subjects originally randomized to the OB arm with virologic failure could switch to a enfuvirtide containing regimen any time after week 8. These subjects were no longer on study drug but continued to be followed on study. A total of 114 subjects originally randomized to the OB regimen switched to a enfuvirtide containing regimen after experiencing virologic failure. Data for these subjects, including adverse event information, were available for up to 12 weeks after switching to enfuvirtide.

Adverse events were also reported for the 114 subjects who were randomized to OB alone but switched to a enfuvirtide containing regimen after week 8. Switch subjects had up to 12 weeks of enfuvirtide exposure at the time of database closure for this study report. Overall, 79% of switch subjects reported at least one adverse event; the most common adverse events were diarrhea (9.6%), bronchitis (9.6%), vomiting (7.9%), fatigue (7.9%), nausea (7.0%), and insomnia (7.0%). Seven percent of switch subjects had a potentially life threatening adverse event; of these only increased lipase was reported in more than one subject. There was a lower incidence of serious adverse events in switch subjects (13%); serious adverse events reported in more than one subject included increased lipase (3) and pyrexia (2). Seven switch subjects had serious adverse events attributed to a study drug including such as injection site abscess, injection site reaction, agranulocytosis, neutropenia, ascites, pyrexia, and increased lipase. The incidence of ISRs in switch subjects (96%) was similar to that seen in subjects originally randomized to enfuvirtide. Eight switch subjects (7.0%) withdrew from the study because of an adverse events; reasons for study withdrawal included ISR (3), gastrointestinal symptoms (2), anxiety, and neuropathy. Finally, one switch subject died due to preexisting cardiomyopathy seven days after starting enfuvirtide. Overall, the incidence and types of adverse events reported for switch subjects were similar to those reported for subjects originally randomized to enfuvirtide.

In summary, the most common adverse event experienced by subjects receiving enfuvirtide in study T20-302 was an injection site reaction. Almost all subjects reported

ISRs and these were common throughout the course of treatment with enfuvirtide. Signs and symptoms of ISRs were often striking, and many subjects reported significant pain or large areas of induration or erythema. In addition, individual ISRs often lasted for several days so that individual subjects had more than one ISR at a time. There were few other adverse events with a higher incidence in the enfuvirtide + OB group than the OB group. When the incidence of adverse events were adjusted for exposure to study drug, the incidence of individual adverse events were often similar between study groups. In addition, many adverse events were consistent with subjects' underlying HIV disease.

C. FDA Analysis of Safety for Studies T20-301 and T20-302

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.

As noted earlier, due to the 2:1 randomization and crossover of OB subjects, exposure time differed substantially between the 2 treatment arms. Because of the difference in exposure between the two treatment groups increases in the incidence of adverse events were only judged to be significant by this reviewer if they were reported in at least 2.5 times as many enfuvirtide recipients. Adverse event data for subjects in the OB group who experienced virologic failure and switched to a enfuvirtide containing regimen ("switch subjects") were collected after the subject switched. Exposure to enfuvirtide ranged from one to 16 weeks in switch subjects. .

> Comment: Since these subjects experienced virologic failure on their OB regimen, as a group they were both at greater risk of a second virologic failure and relatively less immunocompetent at the time of initiating enfuvirtide compared to subjects originally starting the study in the enfuvirtide + OB arm.

Selected adverse events observed at a greater proportion of enfuvirtide + OB recipients in at least one of the Phase 3 studies or toxicities of particular concern are discussed in greater detail in the following sections.

1. **Pancreatitis**

In the applicant's analysis of safety, pancreatitis was reported more frequently in subjects receiving enfuvirtide in study T20-301. Eleven subjects receiving enfuvirtide in T20-301 reported pancreatitis; seven subjects 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. There was not an increase in the incidence of pancreatitis in enfuvirtide recipients in study T20-302; pancreatitis was reported in 7 subjects in the enfuvirtide + OB arm and in 4 subjects in the OB alone arm. There were no cases of pancreatitis in switch subjects of 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). 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.

The incidence of pancreatitis was slightly increased in one of the two studies but not in the other; the severity of pancreatitis as measured by hospitalization was not increased in enfuvirtide recipients. Higher lipase values were observed in enfuvirtide recipients in both studies, consistent with a possible effect of enfuvirtide. Although the overall risk of pancreatitis was low in subjects receiving enfuvirtide, a slightly increased risk of developing pancreatitis in patients receiving enfuvirtide cannot be excluded.

1. **Hepatic toxicity**

Hepatic adverse events, transaminase values (ALT and AST), and bilirubin levels were analyzed for evidence of hepatic toxicity. Increases in AST and ALT reflect hepatocellular damage while increases in bilirubin reflect impaired hepatic function. There was no increase in hepatic adverse events in enfuvirtide recipients in either study. Only hepatomegaly (3 subjects), hepatitis (3 subjects), and fatty liver (2 subjects) were reported in more than one subject in the enfuvirtide + OB arm. 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 10.8 umol/L in the enfuvirtide + OB group and 9.3 umol/L in the OB group. Mean ALT values were higher for subjects in the OB group in T20-301 and similarly higher in the OB arm in study T20-302 (44 vs. 43 U/L in the enfuvirtide + OB arm). Mean AST values were also higher for subjects in the OB group in both studies. Based on these results, there is no evidence of obvious hepatic toxicity associated with enfuvirtide use.

2. Renal toxicity

Renal failure was reported in two subjects in the enfuvirtide + OB group and three in the switch group of study T20-301, compared to no cases of renal failure in the OB group. One episode of renal failure was attributed to dehydration, one to septic shock, and one to use of Amphotericin B. No cases of renal failure were attributed by investigators to the study drug. No episodes of renal failure were reported in study T20-302. Very few subjects in either study had Grade 3 or Grade 4 creatinine values reported, and the mean creatinine values were similar between treatment groups. Although there were an increased number of cases of renal failure reported in study T20-301, it is doubtful that enfuvirtide is associated with significant renal impairment due to the other possible explanations for renal failure, the lack of renal failure in study T20-302, and the small number of subjects with abnormal creatinine levels.

One case of membranoproliferative glomerulonephritis was reported in a enfuvirtide recipient and attributed to enfuvirtide. The presumed mechanism was the formation of immune complexes between enfuvirtide and antibody to gp41. Rare adverse events due to the formation of immune complexes cannot be ruled out in subjects receiving enfuvirtide, and additional data may be necessary to clearly define the risk of immune complex disease with enfuvirtide.

3. Rash

The incidence of adverse events related to the skin was examined in both studies. (This does not include adverse events related to injection site reactions, which are treated separately below and in the appendix.) The incidence of any form of dermatitis or rash was not increased in the enfuvirtide + OB group. There was no increase in the incidence of urticaria, erythema multiforme, or Stevens Johnson syndrome in enfuvirtide recipients.

4. Psychiatric signs and symptoms

Because there were several study discontinuations in study T20-302 for depression, the datasets for both T20-301 and T20-302 were examined for any association between enfuvirtide use and psychiatric adverse events. In study T20-301, there was no difference between the two treatment groups in the number of subjects reporting any psychiatric adverse event, reporting anxiety or reporting stress. Depression was slightly more common in the OB group (10.3% versus 9.8%). There was one serious adverse event in an enfuvirtide-treated subject who was hospitalized due to overwhelming anxiety. However, in study T20-302, more subjects in the enfuvirtide + OB arm compared to the OB arm experienced psychiatric adverse events (81 compared to 28), depression (27 compared to 7), and anxiety/stress (18 compared to 2). The incidence of abnormal dreams and sleep disorders was higher for subjects in the OB arm. Four of these adverse events in the enfuvirtide + OB group were judged as serious by protocol defined criteria: depression (2) and suicide attempt (2). 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. There were no serious psychiatric adverse events reported in the OB group. Six subjects receiving enfuvirtide discontinued the study due to depression and one due to stress.

> Comment: It is unclear why there was a difference in psychiatric adverse events between the two studies. The difference in incidence may be due in part to the difference in study drug exposure. There was no difference in efavirenz use between the two treatment groups in either study. 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.

5. Hypersensitivity reactions

Hypersensitivity reactions associated with enfuvirtide were identified by the sponsor 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. Symptoms subsequently recurred on rechallenge with enfuvirtide; however, symptoms also recurred when the OB regimen 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.

In summary, hypersensitivity reactions were seen in a small number of subjects (<1%) receiving enfuvirtide in studies T20-301 and T20-302, but with diseases related to the formation of immune complexes reported in both studies.

> Comment: The risk of a hypersensitivity reaction associated with enfuvirtide is small 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.

6. Bacterial infections

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 study T20-301 were examined as well as the rate of bacterial infections. There was no 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. The incidence of any infection and of bacterial infections were then analyzed for study T20-302. Results for both studies are shown below in Table 25.

Table 25: 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.

After accounting for the 2:1 randomization, there is still the appearance of an increase in the number of study subjects with bacterial infections in both studies. The specific types of bacterial infections were further identified and are shown in Table 26 for study T20-301. This analysis does not include abscesses or cellulitis at the injection site.

Table 26: Types of Bacterial Infections in Study T20-301

	Enfuvirtide + OB (n=328)		**OB (n=167)**		**Switch (n=81)**	
	# AEs	**# pts**	**# AEs**	**# pts**	**# AEs**	**# pts**
Overall	38	31	6	6	13	9
pneumonia	8	7	1	1	3	3
abscess	6	5				
cellulitis	6	6	3	3	2	2
sepsis/septic shock	5	5			2	2
localized infection	5	5	1	1	1	1

empyema	1	1				
line infection	1	1			2	2
osteomyelitis	1	1				
septic arthritis	1	1				
skin infection	1	1			1	1
Staph infection	1	1		1		
wound infection	1	1				
impetigo	1	1				
bacterial infection					1	1
pyelonephritis					1	1

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

As shown in this table, there was a striking difference in the incidence of certain bacterial infections for subjects in the two treatment groups. Although subjects were randomized 2:1 to enfuvirtide + OB versus OB, the incidence of many bacterial infections was greater than 2.5 fold and the incidence appeared to increase in subjects who switched from OB to an enfuvirtide containing regimen. The increase in the number of subjects receiving enfuvirtide with pneumonia, abscess, cellulitis, sepsis, and localized infections was particularly striking. The types of bacterial infections noted in study T20-302 are shown in Table 27.

Table 27: Types of Bacterial Infections in Study T20-302

	Enfuvirtide + OB (n=335)		OB (n=169)		**Switch (n=114)**	
	# AEs	**# pts**	**# AEs**	**# pts**	**# AEs**	**# pts**
Overall	40	37	10	9	5	4
pneumonia	9	9	1	1	1	1
LRT infection	3	3	1	1		
bronchopneumonia	3	3				
respiratory tract infection	2	2	4	4		
lung infection	1	1				
sepsis/bacteremia	4	4				
cellulitis	4	4				
abscess	3	3			3	3
line infection	2	2				
furuncle	2	2				
localized infection	2	2				
tracheitis	2	2			1	1
osteomyelitis	1	1				
bacterial infection	1	1	1	1		
pyelonephritis	1	1				
wound infection			3	2		

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

Although the terms for adverse events were slightly different in this study, there was again an increase in the incidence of pneumonia and other lower respiratory tract infections, sepsis, abscess, and cellulitis.

In order to further define the scope of this finding, we looked at antibiotic usage, white blood counts, organisms isolated, and mortality. A total of 280 subjects in the enfuvirtide + OB arm of both studies received antibiotics for an adverse event; 122 subjects in the OB arm received antibiotics. After correction for randomization and patient exposure, the rate of antibiotic use was similar between the two treatment groups. There were 278 subjects in the enfuvirtide + OB arm and 165 in the OB arm with a white blood count less than the lower limit of normal; after correction for the two to one randomization, the number of subjects with a low white count was higher in the OB group. There were more subjects in the enfuvirtide + OB arm who had increases in white blood count, but this may have been explained in part by immune reconstitution. The organism causing the bacterial infection was isolated in a minority of infections. There was no predilection for any specific organism or class of organisms. The only organisms isolated in more than one infection were pseudomonas (3) and pneumococcus (2). Finally, there were 8 deaths in the enfuvirtide + OB arm, 5 in the OB arm, and 2 in switch subjects during the first 24 weeks of the two studies. There were no deaths due to bacterial infections in the OB group. Two subjects in the enfuvirtide + OB arm died of bronchopneumonia and two of sepsis; one subject in the switch group died of sepsis. These deaths included one subject who developed pneumonia after aspiration during a seizure and one who was diagnosed with lymphoma and refused treatment of his pneumonia. The organism causing bronchopneumonia was not isolated in either subject. There were a total of three subjects receiving enfuvirtide who developed sepsis: one due to Staphylococcus aureus and Pseudomonas species, one due to Staphylococcus aureus, and one with multiple gram negative organisms after emergency surgery for a perforated colon.

During the review process, this finding was communicated to the applicant. The applicant provided a revised analysis correcting for time of exposure. This is shown in Table 28.

Table 28: 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. After multiple discussions with the applicant, additional data for analyses of this increased rate of pneumonia were submitted; these data are discussed in Section III.

Comment: In summary, an increase in bacterial infections, particularly pneumonia and sepsis, was observed in subjects receiving enfuvirtide in both Phase 3 clinical trials. There was no increase in antibiotic use or neutropenia. There was no predisposition to infection with a particular organism, nor an overall increase in mortality in enfuvirtide recipients. There were 2 deaths due to pneumonia in subjects receiving enfuvirtide, but both subjects had predisposing conditions (aspiration and lymphoma). An additional 3 subjects receiving enfuvirtide died of sepsis. There were no deaths due to bacterial infection in the OB group. The reason for this increased incidence of pneumonia and sepsis in subjects receiving enfuvirtide in the first 24 weeks of studies T20-301 and T20-302 could not be readily explained. This safety signal was further examined with additional data supplied by the applicant; see Section X for further discussion.

7. 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 29 below. This does not include deaths that occurred more than 28 days after stopping study drug.

Table 29: Cause of Death in Studies T20-301 and T20-302

Cause of death (No. of subjects if over 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
sepsis	Switch
advanced AIDS (2)	OB
AIDS encephalopathy	OB
lymphoma	OB
toxoplasmosis	OB

Source: Death datasets from July 16, 2002 submission.

As stated in the previous section, there were 8 deaths in enfuvirtide + OB subjects, five in the OB group, and 2 in switch subjects during the first 24 weeks of the study. After correcting for the 2:1 randomization, there was no difference in the mortality rate between the two groups. There were five deaths due to infection in subjects receiving enfuvirtide; these deaths were discussed in the previous section. 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.

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

In summary, the mortality rate was similar between the treatment groups and the majority of deaths were due to advanced HIV disease and 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 contributing factor in these subjects' disease course.

8. Summary of Enfuvirtide Safety in Studies T20-301 and T20-302

Injection site reactions were by far the most common adverse event experienced by subjects receiving enfuvirtide in studies T20-301 and T20-302. ISRs were seen in almost all subjects and recurred in individual subjects throughout the study. However, complications of these ISRs were uncommon, and subjects were able to continue treatment with enfuvirtide despite the ISRs. Self-injection of enfuvirtide and ISRs may have had a psychological impact on study subjects; more subjects receiving enfuvirtide than receiving OB alone reported anxiety and depression. Pneumonia was reported in more subjects in the enfuvirtide + OB arm than in the OB alone arm; the incidence of pneumonia was also increased in subjects switching from OB to enfuvirtide. The reason for this is unclear, but it did not result in increased mortality. Hypersensitivity reactions were an uncommon adverse event noted in less than 1% of subjects receiving enfuvirtide; although patients and healthcare providers should be educated to recognize the signs and symptoms of hypersensitivity reactions, these reactions are rare. Other adverse events were consistent with the subjects' underlying HIV disease and its treatment.

D. Effect of serum gp41 antibodies on the safety and efficacy of Enfuvirtide

Enfuvirtide is a 36 amino acid peptide; its sequence was based on amino acid residues within the gp41 transmembrane glycoprotein of HIV-1. Enfuvirtide inhibits the fusion of HIV to the host cell membrane by binding to the HIV gp41 protein and preventing the

conformational change of HIV necessary for entry of HIV into CD4-positive cells. Since patients produce antibody to gp41 and this antibody could potentially crossreact with enfuvirtide, all subjects in studies T20-301 and T20-302 had baseline, week 8, and week 24 measurements of gp41 antibody. At baseline, 77% (477/616) of subjects in the enfuvirtide + OB arm and 74% (221/298) in the OB alone arm were positive for gp41 antibody. At week 24, 68% of subjects in the enfuvirtide + OB arm and 79% in the OB alone arm had detectable levels of antibody to gp41.

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

Change in viral load was analyzed by change in gp41 antibody level and no effect was demonstrated. Specifically, an increase in antibody to gp41 did not predispose subjects on enfuvirtide to virologic failure; in contrast, a greater proportion of subjects in the enfuvirtide + OB group had decreases in gp41 antibody from baseline to week 24. Since so few subjects were antibody negative at baseline, efficacy results could not be analyzed for this group. In the safety analysis, no specific adverse event or pattern of adverse events correlated with specific changes in gp41 antibody level. In particular, increases in gp41 antibody levels did not appear to be associated with hypersensitivity reactions or injection site reactions.

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

E. Overall Conclusion

Enfuvirtide was clearly biologically active in both Phase 3 clinical trials. Subjects receiving enfuvirtide had a statistically significant decrease in plasma HIV levels from baseline to week 24 relative to an active control group. Different sensitivity analyses confirmed this robust effect, as did the analyses of all secondary endpoints. Please see Dr. Hammerstrom's statistical review for additional analysis of efficacy. Most adverse events observed in subjects receiving enfuvirtide were consistent with signs and symptoms of HIV infection and its treatment. However, injections site reactions

occurred in almost every subject, and subjects continued to develop ISRs throughout the study. Patients and healthcare providers must be educated about the incidence of and the signs and symptoms of ISRs for effective risk management post approval. Hypersensitivity reactions were rarely seen but did lead to study discontinuation in some subjects and can recur on rechallenge with enfuvirtide. Finally, a relatively incidence of bacterial pneumonia, was observed in subjects receiving enfuvirtide in both studies T20-301 and T20-302. This will be discussed further in Section III.

II. Safety Update Report

A Safety Update Report was submitted on November 15, 2002 and contained additional data for all studies of enfuvirtide that were ongoing at the time of the submission of original NDA submission. The studies included in the Safety Update Report are shown in Table 30.

Table 30: Clinical Studies with Data Included in the Safety Update Report

Type of Study	Study	Number of Subjects (enfuvirtide only)
Phase 3 clinical trials	T20-301, T20-302	663
Continuing access studies	T20-210, T20-211, T20-304	151
Open-label safety studies	T20-305	299
Pharmacokinetic studies	T20-502, T20-503	25
Pediatric studies	T20-204, T20-310	45
Continuing Phase II studies	[redacted]	168

Source: SUR, Table 2, pages 20-24.

A total of 1541 subjects received at least one dose of enfuvirtide as of the cutoff for the safety update. Of these, 1401 have received enfuvirtide at the dose proposed for labeling (90 mg bid in adults and 2.0 mg/kg for children 6 years of age and older). A total of 913 subjects have received enfuvirtide for at least 24 weeks, and 569 subjects have received enfuvirtide for at least 48 weeks.

The data cutoff for the Phase 3 studies, T20-301 and T20-302, in the original NDA was March 6, 2002; the data for the studies in the Safety Update Report was August 12, 2002 allowing for an additional five months follow-up of study subjects. The study design of these two studies resulted in a relatively greater increase in exposure to study drug for the enfuvirtide + OB group compared to the OB group because of subjects with virologic failure in the OB arm switching to an enfuvirtide containing regimen after week 8. (Subjects with virologic failure on the enfuvirtide arm were permitted to remain on enfuvirtide.) As a result, by the time of database closure for the Safety Update Report, exposure to study drug was 3.9 fold higher for subjects in the enfuvirtide + OB arm compared to the OB alone arm. Seventy percent of subjects originally randomized to enfuvirtide + OB versus 20% of subjects on OB alone completed 48 weeks of study on their original randomization by the date of database closure.

Data on AIDS defining events from T20-301 and T20-302 were not included in the original NDA submission but were reported in the update.

Other studies included in the Safety Update Report (see Table 30) included follow-up data from four rollover trials, two Phase 2 trials, and two pediatric trials. The Update also included safety data from three studies that were not included in the original NDA: a large open-label safety study and two pharmacokinetic studies. The database cutoff for all of these studies was July 31, 2002. Preliminary results from NV16471, a study of the pathology of injection site reaction was also contained in this report.

A. General information about safety

The majority of subjects in studies T20-301 and T20-302 reported adverse events. The most frequently reported adverse events were the same as the most frequently reported adverse events in the initial filing: diarrhea, nausea, and fatigue. When corrected for study drug exposure, adverse events reported more commonly in subjects receiving enfuvirtide included peripheral neuropathy, pneumonia, pancreatitis, and decreased appetite. More than 80% of subjects in the enfuvirtide + OB arm and 70% in the OB alone arm experienced treatment-related adverse events. After adjustment for exposure, treatment related adverse events reported more commonly in enfuvirtide recipients included peripheral neuropathy, decreased appetite, depression, and decreased weight.

Potentially life threatening adverse events were noted in 13% of subjects in the enfuvirtide + OB group and in 11% of the OB group; life threatening adverse events reported more commonly in enfuvirtide recipients included pancreatitis, depression, anxiety, and drug hypersensitivity. Thirty percent of subjects in the enfuvirtide + OB arm and 26% in the OB arm had a serious adverse event. The only serious clinical adverse event reported in greater than 2% of subjects in the enfuvirtide + OB group was pancreatitis (2.3%). Grade 4 laboratory values were also classified as serious adverse events; Grade 4 abnormalities reported in more than 2% of subjects included increases in GGT (2.7%) and CPK (2.6%). Serious adverse events were reported in 21% of switch subjects and included pancytopenia, injection site abscess, pulmonary edema, and ascites. Serious adverse events in the rollover studies included deep vein thrombosis, pneumonia, pneumonitis, and diabetes mellitus; serious adverse events reported for the continued Phase 2 studies included neutropenia and drug hypersensitivity; and serious adverse events in the pediatric studies included behavioral disturbance, psychosis, pneumonia, thrombocytopenia, and upper gastrointestinal bleed.

In studies T20-301 and T20-302, similar adverse event terms were collapsed to create selected adverse events of special interest. After adjustment for exposure, adverse events with a higher incidence in enfuvirtide recipients are shown in the following table.

Table 31: Adverse Events of Special Interest with a Higher Incidence in Enfuvirtide Recipients in Studies T20-301 and T20-302

	Events/100 patient years	
	Enfuvirtide + OB	**OB**
peripheral neuropathy	14.5	14.1
hepatic toxicity clinical	2.3	1.2
diabetes mellitus and hypoglycemia	0.042	0.031
bronchospasm and obstruction	2.0	1.2
bone pathology	1.6	1.2
thrombosis and phlebitis	1.1	0.61

Source: SUR, Table 21, page 57.

Time to first episode of all of the events shown in Table 31 were estimated by Kaplan-Meier methodology. These Kaplan-Meier curves showed that the risk of pneumonia did not increase with increasing exposure to enfuvirtide.

Although hepatic toxicity clinical was more common in enfuvirtide recipients, the overall incidence of hepatoxicity was low. Since the increase in clinical hepatic toxicity was not associated with an increased incidence of laboratory toxicity, this finding is likely not significant.

As discussed in Section I.C.5 of this review, psychiatric adverse events were reported more commonly in enfuvirtide recipients in study T20-302 with one successful suicide, two suicide attempts, and six subjects withdrawing from the study because of depression. However, after adjustment for exposure, the rate of depression/suicide in both studies was higher in the OB group than in the enfuvirtide + OB group.

B. Adverse events leading to study withdrawal

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 (9.8 patients/100 patient years) than in the OB alone group (6.7 patients/100 patient years). At the time of the initial filing 44 subjects had discontinued enfuvirtide because of an adverse event; an additional 37 subjects discontinuing prematurely were included in this report. The most common reason for discontinuation was an injection site reaction. Seven subjects discontinued after the initial 24 weeks because of an ISR, and another ten subjects discontinued because of difficulties with self-administration by injection such as being tired of injecting, finding it too demanding, or lack of sites to inject. Other reasons for discontinuation after week 24 were varied and the only reasons observed in more than one subject were pancreatitis (2) and depression (2). For the entire study, the most common reasons for discontinuation were depression (1.1%), vomiting (0.9%), nausea (0.6%), and pancreatitis (0.5%); all other reasons for discontinuation occurred in less than 0.5% of subjects. Eight percent of switch subjects withdrew due to an adverse

event. Reasons for study discontinuation in switch subjects were similar to reasons in subjects originally randomized to enfuvirtide: those observed in more than one subject were ISR (11), pneumonia (2), and lymphoma (2).

Study discontinuations in the rollover studies that were not reported in the initial filing included ISRs (2), nausea and vomiting (1), and carcinoma (1). One additional subject in the pediatric studies discontinued due to cellulitis at the injection site.

The most common reason subjects receiving enfuvirtide discontinued study prematurely was an injection site reaction. Subjects also discontinued because of the difficulties associated with twice daily self-injection. However, the rate of study discontinuation due to ISRs was still relatively low (4%) in spite of the difficulties associated with the subcutaneous injection of enfuvirtide.

C. Injection site reactions

The majority of subjects (98%) in studies T20-301 and T20-302 had injection site reactions; 4.1% discontinued the 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 injection of enfuvirtide. The most frequent signs and symptoms, erythema, induration and nodules/cysts, were the same as reported in the initial filing. There was no evidence of an increase in severity over time for any sign or symptom. There were no additional reports of infection at the injection site.

Information on ISRs was not routinely collected in studies T20-210, T20-211, T20-304, or T20-305 unless the ISR was reported as a serious adverse event. Information was collected in T20-310, but this data was not available for this submission. ISRs were reported in 1.3% of subjects in the continued access studies (T20-210, T20-211, T20-304). One additional subject in the rollover studies and one in the pediatric studies withdrew due to an ISR.

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 [redacted]. 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 [redacted] 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 histologically.

D. Bacterial pneumonia and sepsis

There were 16 additional episodes of bacterial pneumonia reported in the enfuvirtide + OB arm compared to two in the OB arm after the first 24 weeks of studies T20-301 and T20-302. There were three new pneumonias in switch subjects. There was one new episode of sepsis in the enfuvirtide + OB group, one in the switch group, and one in the OB group. The increased incidence of pneumonia in enfuvirtide recipients is partially explained by the 3.9 fold increased exposure for subjects in the enfuvirtide + OB group. See Section III for further discussion.

E. Hypersensitivity reactions

The incidence of hypersensitivity reactions in all subjects receiving enfuvirtide in clinical studies was less than 1%; hypersensitivity reactions did recur on rechallenge in three subjects. All serious adverse events that were suggestive of a hypersensitivity reaction were reviewed by the applicant. Five of these adverse events were judged to be related to enfuvirtide including one subject with rash, fever, and vomiting, one subject with rash, nausea, chills, and hypotension, one subject; with fever, maculopapular rash, and increased transaminases, one subject with primary immune complex reaction, and one with membranoproliferative glomerulonephritis. Three episodes of hypersensitivity recurred on rechallenge with enfuvirtide. On rechallenge, one subject developed rash, fever, and vomiting, one subject developed rash, chills, rigors, and hypotension, and one developed fever with worsening ISR. None of the hypersensitivity reactions were fatal with the initial reaction or on rechallenge.

F. Eosinophilia

The incidence of treatment-emergent eosinophilia in studies T20-301 and T20-302 was 11% in enfuvirtide + OB subjects and 2% in OB subjects. After adjustment for exposure, eosinophilia was still observed at a higher frequency in the enfuvirtide + OB arm (11.5 subjects/100 patient years) compared to the OB arm (4.9 subjects/100 patient years). The incidence of hypersensitivity reactions was similar in subjects with eosinophilia and in those without eosinophilia (20% and 21% respectively). Only one subject with a hypersensitivity reaction had treatment emergent eosinophilia. In addition, there was no difference in the signs and symptoms of ISRs in subjects with eosinophilia or those without eosinophilia. Finally, there was no correlation with change in gp41 antibody titer and eosinophilia. In summary, although eosinophilia was commonly observed in subjects receiving enfuvirtide, it did not appear to correlate with any clinical outcome.

G. Deaths

There have been a total of 46 deaths in subjects receiving enfuvirtide in any clinical study, including nine subjects in studies T20-301 and T20-302 who died more than 28

days after discontinuing enfuvirtide. Twenty-two subjects (3.3%) in studies T20-301 and T20-302 died during the study compared to 6 subjects (2.4%) in the OB arm. Of the 22 subjects who died in the enfuvirtide + OB group, the following causes of death were observed in more than one subject: pneumonia (5), lymphoma (3), and sepsis (2). Other causes included hepatorenal failure, multi-organ failure, pancreatitis, cardiac failure, lactic acidosis, Guillain Barre syndrome and suicide. The deaths from Guillain Barre syndrome and suicide, which were described in the initial filing, were the only deaths attributed to enfuvirtide. Five subjects in the switch group died; causes of death were cerebrovascular accident, cardiomyopathy, advanced HIV disease, lymphoma, and sepsis. Two of these subjects died more than 28 days after their last dose of enfuvirtide. Overall, when corrected for exposure, there was no difference in the mortality rate between the two treatment groups in studies T20-301 and T20-302.

There were two deaths in the rollover studies of enfuvirtide; one due to pneumonia and one to carcinoma. There were no deaths in the pediatric studies.

No single cause of death was noted in subjects receiving enfuvirtide. Death was often due to advanced HIV disease or a complication of HIV infection. Although there were deaths due to pneumonia or sepsis, these subjects had profound immunosuppression and coexisting illnesses at the time of death.

H. AIDS defining events in studies T20-301 and T20-302

All AIDS defining events (ADEs) identified by individual investigators were reviewed by an independent adjudication committee. The committee was blinded to the individual subject's treatment assignment but was provided with details for each ADE. Each ADE was given a grade of A, B, or C. Histologically proven ADEs were given a grade of "A," clinically confirmed ADEs were given a "B," and presumptive diagnoses were given a "C." Only ADEs graded as A or B were included as ADEs in the analysis. All ADE within the first 28 days of the study were excluded to avoid including any ADEs that were present on study entry.

The proportion of subjects with an ADE between the two treatment groups was similar: 6.8% in the enfuvirtide + OB arm and 4.8% in the OB arm. (The greater incidence if the enfuvirtide arm is attributable to greater duration of drug exposure.) The most common ADE in both groups was oral candidiasis, which was reported in 1.8% of subjects in the enfuvirtide + OB arm and in 1.5% of subjects in the OB arm. Other ADEs reported in more than 1% of enfuvirtide recipients were cytomegalovirus and herpes zoster infections.

These studies were not designed to determine the difference in AIDS defining events or death; due to the low rate of ADEs observed with prophylactic medications, a larger sample size, and/or longer duration of study would be necessary to power a study for this endpoint. In addition, clinical endpoints such as AIDS defining events and death are better examined in studies of longer duration. Therefore, it is not of concern that

neither the incidence of AIDS defining events or the mortality rate is significantly lower in enfuvirtide recipients.

I. Adverse events in studies T20-305, T20-502, and T20-503

Since the results of studies T20-305, T20-502, and T20-503 were not provided in the original filing but were included in the Safety Update Report, the results are discussed separately in this review. Study T20-305 is an ongoing open-label safety study of enfuvirtide in 299 treatment experienced adults. Mean exposure to enfuvirtide at the time of the Safety Update Report was 12 weeks. The majority of subjects are white (82%) and male (92%). Mean viral load at baseline was 5.1 $\log_{10}$ copies/ml, and mean CD4 cell count was 29 cells/mm^3.

Only serious adverse events were reported for this study. Serious adverse events were reported in 13% (39) of subjects enrolled in study T20-305. No single serious adverse event was reported in more than 2% of subjects. The most commonly reported serious adverse events were pancreatitis (4 subjects) and pyrexia (4 subjects). Two subjects in study T20-305 have died: one due to recurrent pneumonia and one to carcinoma.

Studies T20-502 and T20-503 were open-label, pharmacokinetic, drug interaction studies in HIV-infected, treatment naïve subjects. Twenty-five subjects were enrolled and received enfuvirtide for seven days. Most subjects in study T20-502 were white (83%) and male (83%). Study T20-503 was conducted at a single center in Thailand, and all subjects were Asian or Pacific Islanders. Seven subjects were female and six male.

Adverse events were reported in 44% of subjects in these two studies. The most frequently reported adverse events in study T20-502 were dizziness (2 subjects) and dermatitis (2 subjects); the most frequently reported adverse events in study T20-503 were taste disturbance (3 subjects) tongue hypoaesthesia (2 subjects), and flatulence (2 subjects). Seven subjects in the two studies experienced treatment related adverse events: dizziness (2), vomiting (2), taste disturbance (2), diarrhea, dermatitis, abdominal pain, and mouth ulceration. ISRs were reported in 85% of subjects; the most common sign and symptom was erythema (61.5%). No severe, life threatening, or serious adverse events were reported, and there were no deaths.

Overall, adverse events reported in these three studies were consistent with those reported in studies T20-301 and T20-302. Adverse events including ISRs were seen less commonly in the two pharmacokinetic studies, but subjects in these studies only received enfuvirtide for seven days. The mean time of exposure to enfuvirtide is relatively short in study T20-305, and more than 10% of subjects have reported serious adverse events and two have died. However, this is a treatment experienced study population with advanced HIV disease as evidenced by the low CD4 cell count at entry.

J. Summary of Safety Update Report

No new or unexpected adverse events were reported in the Safety Update Report; however, a more complete discussion of hypersensitivity reactions and eosinophilia were provided. Hypersensitivity reactions with enfuvirtide were reported in less than 1% of study subjects and in a subgroup of subjects recurred with rechallenge. Eosinophilia was common (11% of subjects in phase 3 studies); however, the presence of eosinophilia did not appear to herald or correlate with any adverse event, including hypersensitivity reaction.

AIDS defining events from studies T20-301 and T20-302 were presented in this report. There was no statistical difference in the incidence of ADE between the two study groups, and there was no difference in time to death or diagnosis of ADE between the two treatment groups. This finding is somewhat surprising given the virological and immunolgical benefit observed in enfuvirtide recipients, but these studies were not powered to determine a difference in ADEs or death. In addition, only the first 24 weeks of data were presented, and differences in ADEs and death are best determined with longer durations of follow-up. Differences may also have been masked by the study design which permitted crossover of virologically 'failing' subjects.

III. Additional Safety Analysis for Studies T20-301 and T20-302

As discussed in Section I.C.7, bacterial pneumonia was reported in a higher proportion of subjects in the enfuvirtide + OB arm (4.68 events/100 patient years) than in the OB arm (0.61 events/100 patient years). In an initial analyses by this reviewer, the increased incidence of pneumonia was not associated with increased mortality, increased antibiotic usage, specific causative organisms, or neutropenia. These findings were discussed with the Applicant, and the Division requested additional information including the submission of all available data for subjects in studies T20-301 and T20-302 since database closure for the Safety Update Report. The Division also requested additional analyses of the data including rates of all bacterial infection and pneumonia, mortality rates for all treatment groups, and determination of risk factors for the development of bacterial pneumonia.

Multiple submissions dated January 29, 30, 31, and February 3, 4, 5, 6, 7, 10, and 14 were received. Information from studies T20-301 and T20-302 was submitted up to closure of the database on January 17, 2003, along with additional analyses of this data and a revised discussion of the risks and benefits associated with enfuvirtide use.

At the database cutoff on January 17, 2003, 72% of subjects in the enfuvirtide + OB arm had completed 48 weeks compared to only 39% of subjects in the OB arm. Total study drug exposure was 813.5 patient years in the enfuvirtide + OB arm, 163.4 patient years in the OB arm, and 213.8 patient years in subjects who switched from OB to an enfuvirtide containing regimen. After adjusting for exposure, the overall incidence of bacterial infections was lower in the enfuvirtide + OB group compared to the OB group.

The incidence of sepsis was slightly higher in enfuvirtide recipients than in subjects in the OB group (1.6 events/100 patient years compared to 1.2 events/100 patient years), but this was not statistically significant. Forty subjects (6.0%) in the enfuvirtide + OB group, 1 in the OB group, and 10 in the switch group developed pneumonia during the studies. After adjustment for exposure, there were 4.86 episodes of pneumonia in enfuvirtide recipients per 100 patient years compared to 0.61 for subjects in the OB group. The risk of developing pneumonia was significantly higher for subjects receiving enfuvirtide (p=0.02).

Twenty-seven of the 50 episodes of pneumonia in enfuvirtide recipients (subjects originally randomized to enfuvirtide and switch subjects) 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.

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 32.

Table 32: 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 at baseline less than 200 cells/mm^3 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. Grades 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. Grades 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).

Time to either a confirmed AIDS defining event or death by week 24 was similar for the two treatment groups. Only 9% of subjects in the enfuvirtide + OB group and 5% in the OB group reported a ADE during the first 48 weeks of the studies; after adjusting for exposure, this was 10.6 events/100 patient years in the enfuvirtide + OB group and 11.1 events/100 patient years in the OB group. The most common ADEs were candidiasis and cytomegalovirus. There was a total of 20 deaths in the enfuvirtide + OB arm, five in the OB arm, and four in switch subjects; after correcting for exposure, there was no significant difference in mortality rates between the treatment groups. As previously discussed, there were three deaths from pneumonia during the study.

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 an 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. 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. Subjects on the enfuvirtide + OB arm who experienced virologic

failure could choose to remain on T-20. 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 fact, 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. If this theory were correct, one would expect that switch subjects would have the highest incidence of pneumonia because they experienced virologic failure with resultant damage to their immune system and increased drug resistance in their infecting virus. However, the incidence of pneumonia was similar in switch and enfuvirtide + OB subjects.

An alternative but related explanation for the increased incidence of pneumonia in the enfuvirtide + OB arm is that this incidence 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. This theory 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 certainly consistent with these studies. The incidence of pneumonia in the OB arm was unusually low, 0.61 cases/100 patient years, and much lower than that reported in the literature.

In summary, the additional data supplied by the applicant confirm the increased incidence of pneumonia in subjects receiving enfuvirtide. 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 have been influenced by the study design or a statistical abnormality instead of to enfuvirtide itself.

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