Does APTIVUS lower the chance of passing HIV to other people?

APTIVUS does not reduce the chance of passing HIV to others through sexual contact, sharing needles, or being exposed to your blood. Continue to practice safer sex. Use a latex or polyurethane condom or other barrier method to lower the chance of sexual contact with any body fluids such as semen, vaginal secretions or blood. Never use or share dirty needles.

Ask your doctor if you have any questions about safer sex or how to prevent passing HIV to other people.

Who should not take APTIVUS?

Do not take APTIVUS if you:

- are allergic to tipranavir or any of the other ingredients in APTIVUS. See the end of this leaflet for a list of major ingredients.
- are allergic to ritonavir (NORVIR®)
- have moderate to severe liver problems
- take any of the following types of medicines because **you could have serious side effects:**
    - Migraine headache medicines called "ergot alkaloids". If you take migraine headache medicines, ask you doctor or pharmacist if any of them are "ergot alkaloids".
    - Halcion® (triazolam)
    - Hismanal® (astemizole)
    - Orap® (pimozide)
    - Propulsid® (cisapride)
    - Seldane® (terfenadine)
    - Versed® (midazolam)
    - Pacenone® (amiodarone)
    - Vascor® (bepridil)
    - Tambocor® (flecainide)
    - Rythmol® (propafenone)
    - Quinaglute dura® (quinidine)

What should I tell my doctor before I take APTIVUS?

Tell your doctor about all of your medical conditions, including if you:

- **have liver problems** or are infected with Hepatitis B or Hepatitis C. These patients may have worsening of their liver disease.
- **are allergic to sulfa medicines.**
- **have hemophilia.** APTIVUS may cause increased bleeding.
- **have diabetes.** APTIVUS may worsen your diabetes or high blood sugar levels.

- **are pregnant or planning to become pregnant.** It is not known if APTIVUS can harm your unborn baby. You and your doctor will need to decide if APTIVUS is right for you. If you take APTIVUS while you are pregnant, talk to your doctor about how you can be in the Antiretroviral Pregnancy Registry.

- **are breast-feeding.** Do not breast-feed if you are taking APTIVUS. You should not breast-feed if you have HIV because of the chance of passing the HIV virus to your baby. Talk with your doctor about the best way to feed your baby.

- **are using estrogens for birth control or hormone replacement.** Women who use estrogens for birth control or hormone replacement have an increased chance of developing a skin rash while taking APTIVUS. If a rash occurs, it is usually mild to moderate, but you should talk to your doctor as you may need to temporarily stop taking either APTIVUS or the other medicine that contains estrogen or female hormones.

Tell your doctor about all the medicines you take including prescription and nonprescription medicines, vitamins and herbal supplements. **APTIVUS and many other medicines can interact. Sometimes serious side effects will happen if APTIVUS is taken with certain other medicines (see "Who should not take APTIVUS?").**

- Some medicines cannot be taken at all with APTIVUS
- Some medicines will require a change in dosage if taken with APTIVUS
- Some medicines will require close monitoring if taken with APTIVUS.

Women taking birth control pills need to use another birth control method. APTIVUS makes birth control pills work less well.

Know all the medicines you take and keep a list of them with you. Show this list to all your doctors and pharmacists anytime you get a new medicine you take. They will tell you if you can take these other medicines with APTIVUS. **Do not start any new medicines while you are taking APTIVUS without first talking with your doctor or pharmacist.** You can ask your doctor or pharmacist for a list of medicines that can interact with APTIVUS.

How should I take APTIVUS?

- Take APTIVUS exactly as your doctor has prescribed. You should check with your doctor or pharmacist if you are not sure. **You must take APTIVUS at the same time as NORVIR® (ritonavir).** The usual dose is 500 mg (two 250 mg capsules) of APTIVUS, together with 200 mg (two 100 mg capsules or 2.5 mL of solution) of NORVIR, twice per day. APTIVUS with NORVIR must be used together with other anti-HIV medicines.

APTIVUS comes in a capsule form and you should **swallow APTIVUS capsules whole. Do not chew the capsules.**

- Always take APTIVUS with food.
- Do not change your dose or stop taking APTIVUS without first talking with your doctor.
- If you take too much APTIVUS, call your doctor or poison control center right away.
- If you forget to take APTIVUS, take the next dose of APTIVUS, together with NORVIR® (ritonavir), as soon as possible. Do not take a double dose to make up for a missed dose.

- It is very important to take all your anti-HIV medicines as prescribed and at the right times of day. This can help your medicines work better. It also lowers the chance that your medicines will stop working to fight HIV (drug resistance).
- When your APTIVUS supply starts to run low, get more from your doctor or pharmacy. This is very important because the amount of virus in your blood may increase if the medicine is stopped for even a short period of time. The HIV virus may develop resistance to APTIVUS and become harder to treat. You should NEVER stop taking APTIVUS or your other HIV medicines without talking with your doctor.

What are the possible side effects of APTIVUS?

APTIVUS may cause serious side effects, including:

- **liver problems, including liver failure and death.** Your doctor should do blood tests to monitor your liver function during treatment with APTIVUS. Patients with liver diseases such as Hepatitis B and Hepatitis C may have worsening of their liver disease with APTIVUS and should have more frequent monitoring blood tests.

- **rash.** Mild to moderate rash, including flat or raised rashes or sensitivity to the sun, have been reported in approximately 10% of subjects receiving APTIVUS. Some patients who developed rash also had joint pain or stiffness, throat tightness, or generalized itching.

- **increased bleeding in patients with hemophilia.** This can happen in patients taking APTIVUS or other protease inhibitor medicines.

- **diabetes and high blood sugar (hyperglycemia).** This can happen in patients taking APTIVUS or other protease inhibitor medicines. Some patients have diabetes before starting treatment with APTIVUS which gets worse. Some patients get diabetes during treatment with APTIVUS. Some patients will need changes in their diabetes medicine. Some patients will need new diabetes medicine.

- **increased blood fat (lipid) levels.** Your doctor should do blood tests to monitor your blood fat (triglycerides and cholesterol) during treatment with APTIVUS. Some patients taking APTIVUS have large increases in triglycerides and cholesterol. The long-term chance of having a heart attack or stroke due to increases in blood fats caused by APTIVUS is not known at this time.

- **changes in body fat.** These changes have happened in patients taking APTIVUS. and other anti-HIV medicines. The changes may include an increased amount of fat in the upper back and neck ("buffalo hump"), breast, and around the back, chest, and stomach area. Loss of fat from the legs, arms, and face may also happen. The cause and long-term health effects of these conditions are not known.

The most common side effects include diarrhea, nausea, vomiting, stomach pain, tiredness and headache. Women taking birth control pills may get a skin rash.

It may be hard to tell the difference between side effects caused by APTIVUS, by the other medicines you are also taking, or by the complications of HIV infection. For this reason it is very important that

you tell your doctor about any changes in your health. You should report any new or continuing symptoms to your doctor right away. Your doctor may be able to help you manage these side effects.

The list of side effects is **not** complete. Ask your doctor or pharmacist for more information.

How should I store APTIVUS?

- Store APTIVUS capsules in a refrigerator at approximately **36°F to 46°F (2°C to 8°C).** Once the bottle is opened, the contents must be used within 60 days. Patients may take the bottle with them for use away from home so long as the bottle remains at a temperature of approximately **59°F to 86°F (15°C to 30°C).** You can write the date of opening the bottle on the label. Do not use after the expiration date written on the bottle.

- **Keep APTIVUS and all medicines out of the reach of children.**

General advice about APTIVUS

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use APTIVUS for a condition for which it was not prescribed. Do not give APTIVUS to other people, even if they have the same condition you have. It may harm them.

This leaflet summarizes the most important information about APTIVUS. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about APTIVUS that is written for health professionals.

For additional information, you may also call Boehringer Ingelheim Pharmaceuticals, Inc. at 1-800-542-6257, or (TTY) 1-800-459-9906. You may also request information through the company website at http://us.boehringer-ingelheim.com.

What are the ingredients in APTIVUS?

Active Ingredient: tipranavir

Major Inactive Ingredients: dehydrated alcohol, polyoxyl 35 castor oil, propylene glycol, mono/diglycerides of caprylic/capric acid and gelatin.

Rx only

Distributed by:
Boehringer Ingelheim Pharmaceuticals, Inc.
Ridgefield, CT 06877 USA

APTIVUS is a registered trademark used under license from Boehringer Ingelheim International GmbH

APTIVUS Capsules are covered by U.S. Patents 5,852,195, 6,147,095, 6,169,181 and 6,231,887

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use FUZEON safely and effectively. See full prescribing information for FUZEON.

FUZEON® (enfuvirtide) for Injection
Initial U.S. Approval: 2003

----------RECENT MAJOR CHANGES----------
Warnings and Precautions, Pneumonia (5.3) 04/2011

---------- INDICATIONS AND USAGE----------
FUZEON is an HIV-1 fusion inhibitor indicated for use in combination with other antiretroviral agents for the treatment of HIV-1 infection in treatment-experienced patients with HIV-1 replication despite ongoing antiretroviral therapy. (1)

----------DOSAGE AND ADMINISTRATION----------
- Adults: Recommended FUZEON dose of 90 mg (1 mL) twice daily injected subcutaneously into the upper arm, anterior thigh, or abdomen. FUZEON should not be injected near any anatomical areas where large nerves course close to the skin. (2.1)
- Pediatric Patients (6 to 16 years of age): Recommended 2 mg/kg twice daily up to a maximum dose of 90 mg twice daily injected subcutaneously. Weight should be monitored periodically and the FUZEON dose should be adjusted accordingly. (2.2)
- FUZEON must only be reconstituted with 1.1 mL of Sterile Water for Injection provided in the Convenience Kit. (2.3)
- Reconstituted FUZEON must be injected immediately or kept refrigerated in the original vial. It must be used within 24 hours. (2.3)

---------- DOSAGE FORMS AND STRENGTHS----------
- Lyophilized powder: 108 mg/vial (3)

---------- CONTRAINDICATIONS ----------
- Hypersensitivity to FUZEON or any of its components. (4)

---------- WARNINGS AND PRECAUTIONS----------
- Injection Site Reaction: 98% of subjects experienced at least one injection site reaction during FUZEON treatment in randomized, controlled, open-label, multicenter trials. Manifestations included pain and discomfort, erythema, nodules and cysts, and ecchymosis. (5.1)
- Biojector® 2000: Administration of FUZEON with Biojector 2000 may result in neuralgia and/or paresthesia, bruising and hematomas. Patients receiving anticoagulants or persons with hemophilia, or other coagulation disorders, may have a higher risk of post-injection bleeding. (5.2)
- Pneumonia: Monitor for signs and symptoms of pneumonia in HIV-infected patients, especially those predisposed to pneumonia (e.g., low initial CD4 cell count). (5.3)
- Hypersensitivity: FUZEON should be discontinued immediately upon signs and symptoms of systemic hypersensitivity reactions. (5.4)
- Immune Reconstitution: Patients treated with combination antiretroviral therapy, including FUZEON, may experience immune reconstitution syndrome requiring further evaluation and treatment. (5.6)

---------- ADVERSE REACTIONS ----------
Most common adverse reactions are local injection site reactions, diarrhea, nausea, and fatigue. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Genentech at 1-888-835-2555 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

---------- DRUG INTERACTIONS----------
- No dose adjustments of FUZEON or the co-administered drug is needed when FUZEON is administered concomitantly with other antiretroviral or non-antiretroviral drugs. (7, 12.3)

---------- USE IN SPECIFIC POPULATIONS ----------
- Pregnancy: No evidence of harm to the fetus was observed in animal reproduction studies and FUZEON should be used only if clearly needed. (8.1)
- Nursing mothers: Do not breast-feed while receiving FUZEON therapy. (8.3)
- Pediatric Use: Safety and pharmacokinetics of FUZEON have not been established in pediatric patients < 6 years of age. Limited efficacy data for pediatric patients ≥ 6 years of age. (8.4)
- Geriatric Use: No data available for patients ≥ 65 years of age. (8.5)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 04/2011

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

FUZEON® in combination with other antiretroviral agents is indicated for the treatment of HIV-1 infection in treatment-experienced patients with evidence of HIV-1 replication despite ongoing antiretroviral therapy.

This indication is based on results from two controlled studies of 48 weeks duration. Subjects enrolled were treatment-experienced adults; many had advanced disease. There are no studies of FUZEON in antiretroviral naive subjects.

2 DOSAGE AND ADMINISTRATION

2.1 Adults

The recommended dose of FUZEON is 90 mg (1 mL) twice daily injected subcutaneously into the upper arm, anterior thigh or abdomen. Each injection should be given at a site different from the preceding injection site, and only where there is no current injection site reaction from an earlier dose. FUZEON should not be injected near any anatomical areas where large nerves course close to the skin, such as near the elbow, knee, groin or the inferior or medial section of the buttocks, skin abnormalities, including directly over a blood vessel, into moles, scar tissue, bruises, or near the navel, surgical scars, tattoos or burn sites. Additional detailed information regarding the administration of FUZEON is described in the FUZEON *Injection Instructions.*

2.2 Pediatric Patients

Insufficient data are available to establish a dose recommendation of FUZEON in pediatric patients below the age of 6 years. In pediatric patients 6 years through 16 years of age, the recommended dosage of FUZEON is 2 mg/kg twice daily up to a maximum dose of 90 mg twice daily injected subcutaneously into the upper arm, anterior thigh or abdomen. Each injection should be given at a site different from the preceding injection site and only where there is no current injection site reaction from an earlier dose. FUZEON should not be injected into moles, scar tissue, bruises or the navel. Table 1 contains dosing guidelines for FUZEON based on body weight. Weight should be monitored periodically and the FUZEON dose adjusted accordingly.

Table 1 Pediatric Dosing Guidelines

Weight		Dose per bid Injection (mg/dose)	Injection Volume (90 mg enfuvirtide per mL)
Kilograms (kg)	Pounds (lbs)		
11.0 to 15.5	24 to 34	27	0.3 mL
15.6 to 20.0	>34 to 44	36	0.4 mL
20.1 to 24.5	>44 to 54	45	0.5 mL
24.6 to 29.0	>54 to 64	54	0.6 mL
29.1 to 33.5	>64 to 74	63	0.7 mL
33.6 to 38.0	>74 to 84	72	0.8 mL
38.1 to 42.5	>84 to 94	81	0.9 mL
≥42.6	>94	90	1.0 mL

2.3 Directions for Use

For more detailed instructions, see FUZEON *Injection Instructions.*

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

Subcutaneous Administration

FUZEON must only be reconstituted with 1.1 mL of Sterile Water for Injection provided in the Convenience Kit. After adding sterile water, the vial should be gently tapped for 10 seconds and then gently rolled between the hands to avoid foaming and to ensure all particles of drug are in contact with the liquid and no drug remains

on the vial wall. The vial should then be allowed to stand until the powder goes completely into solution, which could take up to 45 minutes. Reconstitution time can be reduced by gently rolling the vial between the hands until the product is completely dissolved. Before the solution is withdrawn for administration, the vial should be inspected visually to ensure that the contents are fully dissolved in solution, and that the solution is clear, colorless and without bubbles or particulate matter. If the FUZEON is foamy or jelled, allow more time for it to dissolve. If there is evidence of particulate matter, the vial must not be used and should be returned to the pharmacy.

FUZEON contains no preservatives. Once reconstituted, FUZEON should be injected immediately or kept refrigerated in the original vial until use. Reconstituted FUZEON must be used within 24 hours. The subsequent dose of FUZEON can be reconstituted in advance and must be stored in the refrigerator in the original vial and used within 24 hours. Refrigerated reconstituted solution should be brought to room temperature before injection and the vial should be inspected visually again to ensure that the contents are fully dissolved in solution and that the solution is clear, colorless, and without bubbles or particulate matter.

A vial is suitable for single use only; unused portions must be discarded (see FUZEON *Injection Instructions*).

Patients should contact their healthcare provider for any questions regarding the administration of FUZEON. Information about the self-administration of FUZEON may also be obtained by calling the toll-free number 1-877-4-FUZEON (1-877-438-9366) or at the FUZEON website, www.FUZEON.com. Patients should be taught to recognize the signs and symptoms of injection site reactions and instructed when to contact their healthcare provider about these reactions.

3 DOSAGE FORMS AND STRENGTHS

Lyophilized powder for injection: 108 mg enfuvirtide per vial

4 CONTRAINDICATIONS

FUZEON is contraindicated in patients with known hypersensitivity to FUZEON or any of its components *[see Warnings and Precautions (5.4)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Local Injection Site Reactions (ISRs)

The majority of subjects (98%) receiving FUZEON in randomized, controlled, open-label, multicenter clinical trials had at least one local injection site reaction; ISRs occurred throughout treatment with FUZEON. Manifestations may include pain and discomfort, induration, erythema, nodules and cysts, pruritus, and ecchymosis *[see Adverse Reactions (6)]*. Reactions are often present at more than one injection site. Patients must be familiar with the FUZEON *Injection Instructions* in order to know how to inject FUZEON appropriately and how to monitor carefully for signs or symptoms of cellulitis or local infection.

5.2 Administration with Biojector® 2000

Nerve pain (neuralgia and/or paresthesia) lasting up to 6 months associated with administration at anatomical sites where large nerves course close to the skin, bruising and hematomas have occurred with use of the Biojector 2000 needle-free device for administration of FUZEON. Patients receiving anticoagulants or persons with hemophilia, or other coagulation disorders, may have a higher risk of post-injection bleeding.

5.3 Pneumonia

An increased rate of bacterial pneumonia was observed in subjects treated with FUZEON in the Phase 3 clinical trials compared to the control arm. The incidence of pneumonia was 2.7% or 3.2 events/100 patient-years in subjects receiving FUZEON+background regimen. On analysis of all diagnoses of pneumonia (pneumonia, bacterial pneumonia, bronchopneumonia, and related terms) in T20-301 and T20-302, an increased rate of bacterial pneumonia was observed in subjects treated with FUZEON compared to the control arm (6.9%, 6.7 pneumonia events per 100 patient-years versus 0.6 events per 100 patient-years, respectively). Approximately half of the study subjects with pneumonia required hospitalization. Three subject deaths in the FUZEON arm

were attributed to pneumonia; all three had serious concomitant AIDS-related illnesses that contributed to their deaths. Risk factors for pneumonia included low initial CD4 lymphocyte count, high initial viral load, intravenous drug use, smoking, and a prior history of lung disease.

Because it was unclear whether the higher incidence rate of pneumonia was related to FUZEON use, an observational study in 1850 HIV-infected patients (740 FUZEON treated patients and 1110 non-FUZEON treated patients) was conducted to evaluate the risk of pneumonia in patients treated with FUZEON. A total of 123 patients had a confirmed or probable pneumonia event in this study (62 in the FUZEON treatment arm with 1962 patient-years of observation and 61 in the non-FUZEON treatment arm with 3378 patient-years of observation). The incidence of pneumonia was 3.2 events/100 patient-years in the FUZEON treatment arm and 1.8 events/100 patient-years in the non-FUZEON treatment arm. The hazard ratio, adjusting for other baseline risk factors, was 1.34 (95% C.I. = 0.90 – 2.00). Based on this observational study, it is not possible to exclude an increased risk of pneumonia in patients treated with FUZEON compared to non-FUZEON treated patients.

It is unclear if the increased incidence of pneumonia is related to FUZEON use. However, because of these findings, patients with HIV-1 infection should be carefully monitored for signs and symptoms of pneumonia, especially if they have underlying conditions which may predispose them to pneumonia. Risk factors for pneumonia included low initial CD4 cell count, high initial viral load, intravenous drug use, smoking, and a prior history of lung disease.

5.4 Hypersensitivity Reactions

Systemic hypersensitivity reactions have been associated with FUZEON therapy and may recur on re-challenge. Hypersensitivity reactions have occurred in <1% of subjects studied and have included combinations of: rash, fever, nausea and vomiting, chills, rigors, hypotension, and/or elevated serum liver transaminases. Other adverse events that may be immune mediated and have been reported in subjects receiving FUZEON include primary immune complex reaction, respiratory distress, glomerulonephritis, and Guillain-Barre syndrome. Patients developing signs and symptoms suggestive of a systemic hypersensitivity reaction should discontinue FUZEON and should seek medical evaluation immediately. Therapy with FUZEON should not be restarted following systemic signs and symptoms consistent with a hypersensitivity reaction. Risk factors that may predict the occurrence or severity of hypersensitivity to FUZEON have not been identified.

5.5 Non-HIV Infected Individuals

There is a theoretical risk that FUZEON use may lead to the production of anti-enfuvirtide antibodies which cross react with HIV gp41. This could result in a false positive HIV test with an ELISA assay; a confirmatory western blot test would be expected to be negative. FUZEON has not been studied in non-HIV infected individuals.

5.6 Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including FUZEON. During the initial phase of combination antiretroviral treatment, patients whose immune system responds may develop an inflammatory response to indolent or residual opportunistic infections (such as *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis jirovecii* pneumonia [PCP] or tuberculosis), which may necessitate further evaluation and treatment.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections:

- Administration with Biojector® 2000 *[see Warnings and Precautions (5.2)]*
- Pneumonia *[see Warnings and Precautions (5.3)]*
- Hypersensitivity Reactions *[see Warnings and Precautions (5.4)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The overall safety profile of FUZEON is based on 2131 subjects who received at least 1 dose of FUZEON during various clinical trials. This includes 2051 adults, 658 of whom received the recommended dose for greater than 48 weeks, and 63 pediatric subjects.

Assessment of treatment-emergent adverse events is based on the pooled data from the two randomized, controlled, open-label, multicenter trials in treatment-experienced subjects, T20-301 (TORO 1) and T20-302 (TORO 2).

Local Injection Site Reactions

Local injection site reactions were the most frequent adverse events associated with the use of FUZEON. In T20-301 and T20-302, 98% of subjects had at least one local injection site reaction (ISR). A total of 7% of subjects discontinued treatment with FUZEON because of ISRs (4%) or difficulties with injecting FUZEON (3%) such as injection fatigue and inconvenience. Eighty-five percent of subjects experienced their first ISR during the initial week of treatment; ISRs continued to occur throughout treatment with FUZEON. For most subjects the severity of signs and symptoms associated with ISRs did not change during the 48 weeks of treatment. The majority of ISRs were associated with erythema, induration, the presence of nodules or cysts, and mild to moderate pain at the injection site (Table 2). In addition, the average duration of individual ISRs was between three and seven days in 41% of subjects and more than seven days in 24% of subjects. Also, the numbers of ISRs per subject at any one time was between six to 14 ISRs in 26% of subjects and more than 14 ISRs in 1.3% of subjects. Infection at the injection site (including abscess and cellulitis) was reported in 1.7% of adult subjects.

Table 2 Summary of Individual Signs/Symptoms Characterizing Local Injection Site Reactions to Enfuvirtide in Studies T20-301 and T20-302 Combined (% of Subjects) Through 48 Weeks

	N=663		
Event Category	**Any Severity Grade**	**% of Subjects with Grade 3 Reactions**	**% of Subjects with Grade 4 Reactions**
Pain/Discomfort[a]	96%	11%	0%
Induration	90%	39% >25 but <50 mm	18% ≥50 mm
Erythema	91%	22% >50 but <85 mm	10% ≥85 mm
Nodules and Cysts	80%	23% >3 cm average diameter	0.2% Draining
Pruritus[b]	65%	3%	NA
Ecchymosis	52%	5% >3 but ≤5 cm	2% >5 cm

[a]Grade 3 = severe pain requiring prescription non-topical analgesics or limiting usual activities.
Grade 4 = severe pain requiring hospitalization or prolongation of hospitalization, resulting in death, or persistent or significant disability/incapacity, or life-threatening, or medically significant.
[b]Grade 3 = refractory to topical treatment or requiring oral or parenteral treatment.
Grade 4 = not applicable.

Other Adverse Events

In T20-301 and T20-302, after study week 8, subjects on background alone who met protocol defined criteria for virological failure were permitted to revise their background regimens and add FUZEON. Exposure on FUZEON+background was 557 patient-years, and to background alone 162 patient-years. Due to this difference in exposure, safety results are expressed as the number of patients with an adverse event per 100 patient-years of exposure. For FUZEON+background, adverse events are also displayed by percent of subjects.

The events most frequently reported in subjects receiving FUZEON+background regimen, excluding ISRs, were diarrhea (38 per 100 patient-years or 31.7%), nausea (27 per 100 patient-years or 22.8%), and fatigue (24 per 100 patient-years or 20.2%). These events were also commonly observed in subjects that received background regimen alone: diarrhea (73 per 100 patient-years), nausea (50 per 100 patient-years), and fatigue (38 per 100 patient-years).

Treatment-emergent adverse events, regardless of causality and excluding ISRs, from Phase 3 studies are summarized for adult subjects, in Table 3. Any Grade 2 or above events occurring at ≥2 percent of subjects and at a higher rate in subjects treated with FUZEON are summarized in Table 3; events that occurred at a higher rate in the control arms are not displayed.

Rates of adverse events for subjects who switched to FUZEON after virological failure were similar.

Table 3 Rates of Treatment-Emergent Adverse Events* (≥Grade 2) Reported in ≥2% of Subjects Treated with FUZEON (Pooled Studies T20-301/T20-302 at 48 Weeks)**

Adverse Event (by System Organ Class)	**FUZEON+ Background Regimen (N=663)**	**FUZEON+ Background Regimen (N=663)**	**Background Regimen (N=334)**
	663 subjects total	557 total patient-years	162 total patient-years
	% frequency	rate/100 patient-years	rate/100 patient-years
Weight Decreased	6.6%	7.9	6.2
Sinusitis	6.0%	7.2	4.9
Abdominal Pain	3.9%	4.7	3.7
Cough	3.9%	4.7	2.5
Herpes Simplex	3.5%	4.1	3.7
Appetite Decreased	3.2%	3.8	2.5
Pancreatitis	3.0%	3.6	2.5
Pain in Limb	2.9%	3.4	3.1
Pneumonia (see text below)	2.7%	3.2	0.6
Myalgia	2.7%	3.2	1.2
Influenza-Like Illness	2.4%	2.9	1.9
Folliculitis	2.4%	2.9	2.5
Anorexia	2.3%	2.7	1.9
Dry Mouth	2.1%	2.5	1.9
Conjunctivitis	2.0%	2.3	1.9

*Excludes Injection Site Reactions
**Events listed occurred more frequently in subjects treated with FUZEON (based on rates/100 patient-years).

Less Common Events

The following adverse events have been reported in 1 or more subjects; however, a causal relationship to FUZEON has not been established.

Immune System Disorders: worsening abacavir hypersensitivity reaction

Renal and Urinary Disorders: glomerulonephritis; tubular necrosis; renal insufficiency; renal failure (including fatal cases)

Blood and Lymphatic Disorders: thrombocytopenia; neutropenia; fever; lymphadenopathy

Endocrine and Metabolic: hyperglycemia

Infections: sepsis; herpes simplex

Nervous System Disorders: taste disturbance; Guillain-Barre syndrome (fatal); sixth nerve palsy; peripheral neuropathy

Cardiac Disorders: unstable angina pectoris

Gastrointestinal Disorders: constipation; abdominal pain upper

General: asthenia

Hepatobiliary Disorders: toxic hepatitis; hepatic steatosis

Investigations: increased amylase; increased lipase; increased AST; increased GGT; increased triglycerides

Psychiatric Disorders: insomnia; depression; anxiety; suicide attempt

Respiratory, Thoracic, and Mediastinal Disorders: pneumopathy; respiratory distress; cough

Skin and Subcutaneous Tissue Disorders: pruritus

Laboratory Abnormalities

Table 4 shows the treatment-emergent laboratory abnormalities that occurred in at least 2 subjects per 100 patient-years and more frequently in those receiving FUZEON+background regimen than background regimen alone from T20-301 and T20-302.

Table 4 Treatment-Emergent Laboratory Abnormalities in ≥2% of Subjects Receiving FUZEON* (Pooled Studies T20-301 and T20-302 at 48 Weeks)

Laboratory Parameters	Grading	FUZEON+ Background Regimen (N=663)	FUZEON+ Background Regimen (N=663)	Background Regimen (N=334)
		663 subjects total	557 total patient-years	162 total patient-years
		% frequency	rate/100 patient-years	rate/100 patient-years
Eosinophilia				
1-2 X ULN (0.7 x 10^9/L)	0.7-1.4 x 10^9/L	9.1%	10.8	3.7
>2 X ULN (0.7 x 109/L)	>1.4 x 10^9/L	1.8%	2.2	1.8
ALT				
Grade 3	>5-10 x ULN	4.1%	4.8	4.3
Grade 4	>10 x ULN	1.2%	1.4	1.2
Creatine Phosphokinase (U/L)				
Grade 3	>5-10 x ULN	6.9%	8.3	8.0
Grade 4	>10 x ULN	2.6%	3.1	8.6

*Events listed occurred more frequently in subjects treated with FUZEON (based on rates/100 patient-years).

Adverse Events in Pediatric Patients

FUZEON has been studied in 63 pediatric subjects 5 through 16 years of age with duration of FUZEON exposure ranging from 1 dose to 134 weeks. Adverse experiences seen during clinical trials were similar to those observed in adult subjects, although infections at site of injection (cellulitis or abscess) were more frequent in adolescents than in adults, with 4 events occurring in 3 of 28 (11%) subjects.

7 DRUG INTERACTIONS

See also Clinical Pharmacology (12.3)

7.1 Potential for FUZEON to Affect Other Drugs

Based on the results from an *in vitro* human microsomal study, enfuvirtide is not an inhibitor of CYP450 enzymes. In an *in vivo* human metabolism study (N=12), FUZEON at the recommended dose of 90 mg twice daily did not alter the metabolism of CYP3A4, CYP2D6, CYP1A2, CYP2C19 or CYP2E1 substrates.

7.2 Potential for Other Drugs to Affect Enfuvirtide

Based on the available data, co-administration of FUZEON and other drugs which are inducers or inhibitors of CYP450 is not expected to alter the pharmacokinetics of enfuvirtide. No dose adjustments are needed when FUZEON is co-administered with other antiretroviral and non-antiretroviral drugs.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

Reproduction studies have been performed in rats and rabbits at doses up to 27 times and 3.2 times the adult human dose on a m^2 basis and have revealed no evidence of impaired fertility or harm to the fetus due to enfuvirtide. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Antiretroviral Pregnancy Registry

To monitor maternal-fetal outcomes of pregnant women exposed to FUZEON and other antiretroviral drugs, an Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register patients by calling 1-800-258-4263.

8.3 Nursing Mothers

The Centers for Disease Control and Prevention recommends that HIV-infected mothers not breast-feed their infants to avoid the risk of postnatal transmission of HIV. It is not known whether enfuvirtide is excreted in human milk. Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, **mothers should be instructed not to breast-feed if they are receiving FUZEON.**

Studies where radio-labeled ^{3}H-enfuvirtide was administered to lactating rats indicated that radioactivity was present in the milk. It is not known whether the radioactivity in the milk was from radio-labeled enfuvirtide or from radio-labeled metabolites of enfuvirtide (i.e., amino acids and peptide fragments).

8.4 Pediatric Use

The safety and pharmacokinetics of FUZEON have been evaluated in the age groups of 6 to 16 years of age supported by evidence from adequate and well-controlled studies of FUZEON in adults. Limited efficacy data are available in pediatric subjects 6 years of age and older *[see Clinical Pharmacology (12.3)]*.

Sixty-three HIV-1 infected pediatric subjects ages 5 through 16 years have received FUZEON in two open-label, single-arm clinical trials. Adverse experiences, including ISRs, were similar to those observed in adult subjects.

T20-204 was an open-label, multicenter trial that evaluated the safety and antiviral activity of FUZEON in treatment-experienced pediatric subjects. Eleven subjects from 6 to 12 years were enrolled (median age of 9 years). Median baseline CD4 cell count was 495 cells/μL and the median baseline HIV-1 RNA was 4.6 $\log_{10}$ copies/mL.

Ten of the 11 study subjects completed 48 weeks of chronic therapy. At week 48, 6/11 (55%) subjects had ≥1 $\log_{10}$ decline in HIV-1 RNA and 4/11 (36%) subjects were below 400 copies/mL of HIV-1 RNA. The median changes from baseline (for the As Treated population) in HIV-1 RNA and CD4 cell count were -1.48 $\log_{10}$ copies/mL and +122 cells/μL, respectively.

T20-310 was an open-label, multicenter trial that evaluated the pharmacokinetics, safety, and antiviral activity of FUZEON in treatment-experienced pediatric subjects and adolescents. Fifty-two subjects from 5 through 16 years were enrolled (median age of 12 years). Median baseline CD4 cell count was 117 cells/μL and the median baseline HIV-1 RNA was 5.0 $\log_{10}$ copies/mL.

Thirty-two of the 52 study subjects completed 48 weeks of chronic therapy. At week 48, 17/52 (33%) of subjects had ≥1 $\log_{10}$ decline in HIV-1 RNA, 11/52 (21%) of subjects were below 400 copies/mL of HIV-1 RNA and 5/52 (10%) were below 50 copies/mL. The median changes from baseline (for the As Treated population) in HIV-1 RNA and CD4 cell count were -1.17 $\log_{10}$ copies/mL and +106 cells/μL, respectively.

8.5 Geriatric Use

Clinical studies of FUZEON did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, appropriate caution should be exercised in the administration and monitoring of FUZEON in elderly patients reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

8.6 Use in Patients with Hepatic Impairment

No dose adjustments of enfuvirtide are needed in patients with hepatic impairment *[see Clinical Pharmacology (12.3)]*.

8.7 Use in Patients with Renal Impairment

No dose adjustments of enfuvirtide are needed in patients with renal impairment *[see Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

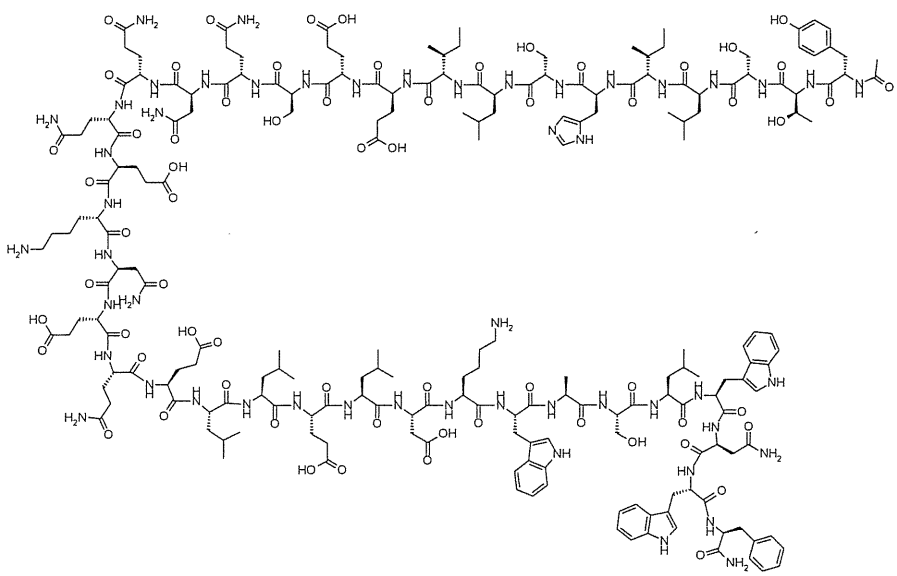
There are no reports of human experience of acute overdose with FUZEON. The highest dose administered to 12 subjects in a clinical trial was 180 mg as a single dose subcutaneously. There is no specific antidote for overdose with FUZEON. Treatment of overdose should consist of general supportive measures.

11 DESCRIPTION

FUZEON (enfuvirtide) is an inhibitor of the fusion of HIV-1 with CD4 cells. Enfuvirtide is a linear 36-amino acid synthetic peptide with the N-terminus acetylated and the C-terminus is a carboxamide. It is composed of naturally occurring L-amino acid residues.

Enfuvirtide is a white to off-white amorphous solid. It has negligible solubility in pure water and the solubility increases in aqueous buffers (pH 7.5) to 85-142 g/100 mL. The empirical formula of enfuvirtide is $C_{204}H_{301}N_{51}O_{64}$, and the molecular weight is 4492. It has the following primary amino acid sequence:

CH_3CO-Tyr-Thr-Ser-Leu-Ile-His-Ser-Leu-Ile-Glu-Glu-Ser-Gln-Asn-Gln-Gln-Glu-Lys-Asn-Glu-Gln-Glu-Leu-Leu-Glu-Leu-Asp-Lys-Trp-Ala-Ser-Leu-Trp-Asn-Trp-Phe-NH_2 and the following structural formula:



The drug product, FUZEON (enfuvirtide) for Injection, is a white to off-white, sterile, lyophilized powder. Each single-use vial contains 108 mg of enfuvirtide for the delivery of 90 mg. Prior to subcutaneous administration, the contents of the vial are reconstituted with 1.1 mL of Sterile Water for Injection giving a volume of approximately 1.2 mL to provide the delivery of 1 mL of the solution. Each 1 mL of the reconstituted solution contains approximately 90 mg of enfuvirtide with approximate amounts of the following excipients: 22.55 mg of mannitol, 2.39 mg of sodium carbonate (anhydrous), and sodium hydroxide and hydrochloric acid for pH adjustment as needed. The reconstituted solution has an approximate pH of 9.0.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Enfuvirtide is an antiviral drug *[see Clinical Pharmacology (12.4)]*.

12.3 Pharmacokinetics

The pharmacokinetic properties of enfuvirtide were evaluated in HIV-1 infected adult and pediatric subjects.

Absorption

Following a 90-mg single subcutaneous injection of FUZEON into the abdomen in 12 HIV-1 infected subjects, the mean (±SD) C_{max} was 4.59 ± 1.5 μg/mL, AUC was 55.8 ± 12.1 μg•h/mL and the median T_{max} was 8 hours (ranged from 3 to 12 h). The absolute bioavailability (using a 90-mg intravenous dose as a reference) was 84.3% ± 15.5%. Following 90-mg twice daily dosing of FUZEON subcutaneously in combination with other antiretroviral agents in 11 HIV-1 infected subjects, the mean (±SD) steady-state C_{max} was 5.0 ± 1.7 μg/mL, C_{trough} was 3.3 ± 1.6 μg/mL, $AUC_{0\text{-}12h}$ was 48.7 ± 19.1 μg•h/mL, and the median T_{max} was 4 hours (ranged from 4 to 8 h).

Absorption of the 90-mg dose was comparable when injected into the subcutaneous tissue of the abdomen, thigh or arm.

Distribution

The mean (±SD) steady-state volume of distribution after intravenous administration of a 90-mg dose of FUZEON (N=12) was 5.5 ± 1.1 L.

Enfuvirtide is approximately 92% bound to plasma proteins in HIV-infected plasma over a concentration range of 2 to 10 μg/mL. It is bound predominantly to albumin and to a lower extent to α-1 acid glycoprotein.

The CSF levels of enfuvirtide (measured from 2 hours to 18 hours after administration of enfuvirtide) in 4 HIV-infected subjects were below the limit of quantification (0.025 μg/mL).

Metabolism/Elimination

As a peptide, enfuvirtide is expected to undergo catabolism to its constituent amino acids, with subsequent recycling of the amino acids in the body pool.

Mass balance studies to determine elimination pathway(s) of enfuvirtide have not been performed in humans.

In vitro studies with human microsomes and hepatocytes indicate that enfuvirtide undergoes hydrolysis to form a deamidated metabolite at the C-terminal phenylalanine residue, M3. The hydrolysis reaction is not NADPH dependent. The M3 metabolite is detected in human plasma following administration of enfuvirtide, with an AUC ranging from 2.4% to 15% of the enfuvirtide AUC.

Following a 90-mg single subcutaneous dose of enfuvirtide (N=12) the mean ±SD elimination half-life of enfuvirtide is 3.8 ± 0.6 h and the mean ±SD apparent clearance was 24.8 ± 4.1 mL/h/kg. Following 90-mg twice daily dosing of FUZEON subcutaneously in combination with other antiretroviral agents in 11 HIV-1 infected subjects, the mean ±SD apparent clearance was 30.6 ± 10.6 mL/h/kg.

Special Populations

Hepatic Impairment

Formal pharmacokinetic studies of enfuvirtide have not been conducted in subjects with hepatic impairment.

Renal Impairment

Analysis of plasma concentration data from subjects in clinical trials indicated that the clearance of enfuvirtide is not affected in patients with creatinine clearance greater than 35 mL/min. The results of a renal impairment

study indicate clearance of enfuvirtide was reduced by 38% in subjects with severe renal impairment (CL = 11 – 35 mL/min; n = 4) and by 14 - 28% in subjects with end-stage renal disease maintained on dialysis (n = 8) compared to subjects with normal renal function (CL >80 mL/min; n = 8). Hemodialysis did not significantly alter enfuvirtide clearance.

No dose adjustment is recommended for patients with impaired renal function.

Gender and Weight

Analysis of plasma concentration data from subjects in clinical trials indicated that the clearance of enfuvirtide is 20% lower in females than males after adjusting for body weight.

Enfuvirtide clearance decreases with decreased body weight irrespective of gender. Relative to the clearance of a 70-kg male, a 40-kg male will have 20% lower clearance and a 110-kg male will have a 26% higher clearance. Relative to a 70-kg male, a 40-kg female will have a 36% lower clearance and a 110-kg female will have the same clearance.

No dose adjustment is recommended for weight or gender.

Race

Analysis of plasma concentration data from subjects in clinical trials indicated that the clearance of enfuvirtide was not different in Blacks compared to Caucasians. Other pharmacokinetic studies suggest no difference between Asians and Caucasians after adjusting for body weight.

Pediatric Patients

The pharmacokinetics of enfuvirtide have been studied in 23 pediatric subjects aged 6 through 16 years at a dose of 2 mg/kg. Enfuvirtide pharmacokinetics were determined in the presence of concomitant medications including antiretroviral agents. A dose of 2 mg/kg twice daily (maximum 90 mg twice daily) provided enfuvirtide plasma concentrations similar to those obtained in adult subjects receiving 90 mg twice daily.

In the 23 pediatric subjects receiving the 2 mg/kg twice daily dose, the mean ±SD steady-state AUC was 56.3 ± 22.3 μg•h/mL, C_{max} was 6.3 ± 2.4 μg/mL, C_{trough} was 3.1 ± 1.5 μg/mL, and apparent clearance was 40 ± 17 mL/h/kg *[see Use in Specific Populations (8.4)]*.

Geriatric Patients

The pharmacokinetics of enfuvirtide have not been studied in patients over 65 years of age.

Drug Interactions

See also Drug Interactions (7)

Table 5 shows the results of the drug-drug interaction studies conducted between FUZEON and the following drugs: ritonavir, saquinavir/ritonavir, and rifampin.

Table 5 Effect of Ritonavir, Saquinavir/Ritonavir, and Rifampin on the Steady-State Pharmacokinetics of Enfuvirtide (90 mg bid)*

Coadministered Drug	Dose of Coadministered Drug	N	% Change of Enfuvirtide Pharmacokinetic Parameters†x (90% CI)		
			C_{max}	AUC	C_{trough}
Ritonavir	200 mg, q12h, 4 days	12	↑24 (↑9 to ↑41)	↑22 (↑8 to ↑37)	↑14 (↑2 to ↑28)
Saquinavir/ Ritonavir	1000/100 mg, q12h, 4 days	12	⇔	↑14 (↑5 to ↑24)	↑26 (↑17 to↑35)
Rifampin	600 mg, qd, 10 days	12	⇔	⇔	↓15 (↓22 to ↓7)

* All studies were performed in HIV-1+ subjects using a sequential crossover design.
† ↑= Increase; ↓ = Decrease; ⇔ = No Effect (↑ or ↓ <10%)
x No interactions were clinically significant.

12.4 Microbiology

Mechanism of Action

Enfuvirtide interferes with the entry of HIV-1 into cells by inhibiting fusion of viral and cellular membranes. Enfuvirtide binds to the first heptad-repeat (HR1) in the gp41 subunit of the viral envelope glycoprotein and prevents the conformational changes required for the fusion of viral and cellular membranes.

Antiviral Activity in Cell Culture

The antiviral activity of enfuvirtide was assessed by infecting different CD4 cell types with laboratory and clinical isolates of HIV-1. The geometric mean EC_{50} value for baseline clinical isolates was 3.52 nM (ranged from 0.089 to 107 nM; 0.4 to 480 ng/mL) by the cMAGI assay (n=130) and was 57.9 nM (1.56 to 1680 nM; 7 to 7530 ng/mL) by a recombinant phenotypic entry assay (n=627). Enfuvirtide was similarly active in cell culture against clades A, AE, C, D, E, F, and G (geometric mean EC_{50} value was 7.7 nM; range 3.9 to 28.6 nM), and R5, X4, and dual tropic viruses. Enfuvirtide has no activity against HIV-2.

Enfuvirtide exhibited additive to synergistic effects in cell culture assays when combined with individual members of various antiretroviral classes, including lamivudine, zidovudine, indinavir, nelfinavir, and efavirenz.

Drug Resistance

HIV-1 isolates with reduced susceptibility to enfuvirtide have been selected in cell culture. Genotypic analysis of these resistant isolates showed mutations that resulted in amino acid substitutions at the enfuvirtide binding HR1 domain positions 36 to 38 of the HIV-1 envelope glycoprotein gp41. Phenotypic analysis of site-directed mutants in positions 36 to 38 in an HIV-1 molecular clone showed a 5-fold to 684-fold decrease in susceptibility to enfuvirtide.

In clinical trials, HIV-1 isolates with reduced susceptibility to enfuvirtide have been recovered from subjects failing a FUZEON containing regimen. Posttreatment HIV-1 virus from 277 subjects experiencing protocol defined virological failure at 48 weeks exhibited a median decrease in susceptibility to enfuvirtide of 33.4-fold (range 0.4-6318-fold) relative to their respective baseline virus. Of these, 249 had decreases in susceptibility to enfuvirtide of greater than 4-fold and all but 3 of those 249 exhibited genotypic changes in the codons encoding gp41 HR1 domain amino acids 36 to 45. Substitutions in this region were observed with decreasing frequency at amino acid positions 38, 43, 36, 40, 42, and 45. Mutations or polymorphisms in other regions of the envelope (e.g., the HR2 region or those yet to be identified) as well as co-receptor usage and density may affect susceptibility to enfuvirtide.

Cross-resistance

HIV-1 clinical isolates resistant to nucleoside analogue reverse transcriptase inhibitors (NRTI), non-nucleoside analogue reverse transcriptase inhibitors (NNRTI), and protease inhibitors (PI) were susceptible to enfuvirtide in cell culture.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Long-term animal carcinogenicity studies of enfuvirtide have not been conducted.

Mutagenesis

Enfuvirtide was neither mutagenic nor clastogenic in a series of *in vivo* and *in vitro* assays including the Ames bacterial reverse mutation assay, a mammalian cell forward gene mutation assay in AS52 Chinese Hamster ovary cells or an *in vivo* mouse micronucleus assay.

Impairment of Fertility

Enfuvirtide produced no adverse effects on fertility in male or female rats at doses up to 1.6 times the maximum recommended adult human daily dose on a m^2 basis.

14 CLINICAL STUDIES

14.1 Description of Clinical Studies

Studies in Antiretroviral Experienced Patients

T20-301 and T20-302 were randomized, controlled, open-label, multicenter trials in HIV-1 infected subjects. Subjects were required to have either (1) viremia despite 3 to 6 months prior therapy with a nucleoside reverse transcriptase inhibitor (NRTI), non-nucleoside reverse transcriptase inhibitor (NNRTI), and protease inhibitor (PI) or (2) viremia and documented resistance or intolerance to at least one member in each of the NRTI, NNRTI, and PI classes.

All subjects received an individualized background regimen consisting of 3 to 5 antiretroviral agents selected on the basis of the subject's prior treatment history and baseline genotypic and phenotypic viral resistance measurements. Subjects were then randomized at a 2:1 ratio to FUZEON 90 mg twice daily with background regimen or background regimen alone.

After week 8, subjects on either treatment arm who met protocol defined criteria for virological failure were permitted to revise their background regimens; those on background regimen alone were also permitted to add FUZEON.

Demographic characteristics for studies T20-301 and T20-302 are shown in Table 6. Subjects had prior exposure to a median of 12 antiretrovirals for a median of 7 years.

Table 6 T20-301 and T20-302 Pooled Subject Demographics

	FUZEON+Background Regimen N=663	Background Regimen N=334
Sex Male Female	 90% 10%	 90% 10%
Race White Black	 89% 8%	 89% 7%
Mean Age (yr) (range)	42 (16-67)	43 (24-82)
Median Baseline HIV-1 RNA (log_{10} copies/mL) (range)	5.2 (3.5-6.7)	5.1 (3.7-7.1)
Median Baseline CD4 Cell Count (cells/mm^3) (range)	89 (1-994)	97 (1-847)

The disposition and efficacy outcomes of T20-301 and T20-302 are shown in Table 7.

Table 7 Outcomes at Week 48 (Pooled Studies T20-301 and T20-302)

Outcomes	FUZEON+Background Regimen 90 mg bid N=663	Background Regimen N=334	
Virological Responder (at least 1 log_{10} below baseline)	304 (46%)	61 (18%)	
Virological Non-responder: • Switch • Completed 48 weeks randomized regimen*	0 191 (29%)	220 (66%) 12 (4%)	
		Continued Background Regimen (N=112)	Switched to FUZEON (N=220)
Discontinued due to insufficient treatment response#	37 (5%)	13 (12%)	22 (10%)
Discontinued due to adverse reactions/intercurrent illness/labs	46 (7%)	9 (8%)	13 (6%)
Deaths	15 (2%)	5 (4%)	2 (1%)
Discontinued due to injection: • Injection site	27 (4%)	NA	10 (5%)