

HIV Med. 2007 Oct;8(7):427-32.

A large prospective study assessing injection site reactions, quality of life and preference in patients using the Biojector vs standard needles for enfuvirtide administration.

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OBJECTIVES: To determine the severity of injection site reactions (ISRs), patient quality of life (QoL) and preference when enfuvirtide is administered by the Biojector (Bioject, Medical Technologies, Inc., Tualatin, OR, USA) relative to standard needles. **METHODS:** A total of 201 HIV-positive patients on stable enfuvirtide-based therapy (n=184) or initiating such therapy (n=17) were evaluated prospectively after switching from standard needles to the Biojector system. Patients used needles for a minimum of 2 weeks prior to switching to the Biojector. Questionnaires to assess the incidence and severity of ISRs (31-item score) and QoL [Medical Outcomes Study HIV Health Survey (MOS-HIV)] were administered at baseline and following a minimum of 14 days of Biojector use. **RESULTS:** The median changes in ISR score and number of ISRs following a median of 1.0 month [interquartile range (IQR) 0.9, 1.3] of Biojector use were -3 (IQR -7, 1) and -1 (IQR -3, 1), respectively. The severity of pain (P<0.0001), induration (P<0.0001), pruritus (P<0.0001), nodules (P<0.0001) and erythema (P<0.0001) all decreased with the Biojector. Administration of enfuvirtide with the Biojector was associated with an improved patient QoL (P<0.0001), and was preferred by 72% of patients. **CONCLUSIONS:** Compared with needles, the Biojector was associated with a decreased severity of ISRs and improved QoL in patients taking enfuvirtide.

Pharmacotherapy. 2006 Dec;26(12):1679-86.

Pharmacokinetic bioequivalence of enfuvirtide using a needle-free device versus standard needle administration.

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STUDY OBJECTIVES: To compare the relative bioavailability of enfuvirtide, a human immunodeficiency virus type 1 (HIV-1) fusion inhibitor, injected with the Biojector 2000 (B2000) needle-free device versus a 27-gauge half-inch needle-syringe; and to assess safety, tolerability, and patient preference for the two devices. **DESIGN:** Open-label, randomized, two-period crossover bioequivalence evaluation. **SETTING:** Clinical research center. **PATIENTS:** Twenty-seven adults with HIV-1 viral loads below 1000 copies/ml. **INTERVENTION:** Each patient received enfuvirtide 90 mg subcutaneously with the B2000 and with the needle-syringe, with a 1-week washout between treatments. **MEASUREMENTS AND MAIN RESULTS:** Twenty-six and 27 patients were included in the bioequivalence and safety analyses, respectively. Plasma enfuvirtide concentrations were measured at baseline and at several intervals after each injection. The B2000:needle-syringe ratios of maximum

concentration (C(max)), area under the concentration-time curve from time zero extrapolated to infinity (AUC(0-infinity)), and AUC from time zero to tau (dosing interval) (AUC(0-tau)) served as criteria for bioequivalence determination. The two drug delivery systems were considered bioequivalent if the 90% confidence intervals (CIs) for the ratios were within 0.8-1.25. Safety and tolerability were evaluated based on documentation of adverse events, graded laboratory toxicities, and local injection-site reactions. Patient surveys provided feedback on device preference. Ratios of C(max), AUC(0-infinity), and AUC(0-tau) were 0.95 (90% CI 0.84-1.09), 0.99 (90% CI 0.93-1.05), and 0.99 (90% CI 0.93-1.05), respectively. The frequency of injection-site reactions was low, and severity was generally mild for both devices. Survey results showed 18 patients (69%) had a positive overall impression of the B2000 and 14 (54%) felt safer injecting with this device. Overall, 17 patients (65%) preferred the B2000 over the needle-syringe. **CONCLUSION:** Bioavailability of enfuvirtide with the B2000 and needle-syringe was equivalent based on C(max), AUC(0-tau), and AUC(0-infinity). Safety profiles and injection-site reactions were comparable between the devices, but patients preferred the B2000. Delivery of enfuvirtide with the B2000 is a feasible alternative to standard needle administration and warrants further evaluation.

AIDS. 2006 Mar 21;20(5):719-23.

Enfuvirtide plasma levels and injection site reactions using a needle-free gas-powered injection system (Biojector).

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OBJECTIVES: To assess the use of the Biojector B2000 needle-free gas-powered injection system for subcutaneous administration of enfuvirtide in HIV-infected patients and to compare this system with standard needles and syringes with respect to ease of use, severity of injection site reactions (ISR), and enfuvirtide plasma levels. **DESIGN:** An observational study among 32 treatment-experienced HIV clinic patients receiving enfuvirtide. **METHODS:** Adult patients were assessed before and after switching from standard needles to the Biojector for enfuvirtide administration. Patients used the Biojector for up to 24 weeks and rated ease of use from 0 (easy) to 3 (difficult). ISR were graded from 0 to 31 for signs and symptoms (erythema, induration, pruritus, nodules/cysts, ecchymosis), duration of individual lesions, and number of lesions. Plasma was collected pre-dose and 1 h post-dose for enfuvirtide measurement. The high-pressure liquid chromatography with tandem mass spectrometry method used was specific for enfuvirtide over its known plasma metabolite. Wilcoxon rank sum tests were used to compare needle-based and Biojector outcomes. **RESULTS:** The Biojector was rated as being significantly easier to use ($P < 0.001$) and reduced the occurrence of ISR compared with standard needles ($P < 0.001$). Enfuvirtide plasma levels were not statistically different between the two administration methods at either pre-dose trough ($P = 0.41$) or 1 h post-dose ($P = 0.74$). **CONCLUSIONS:** The Biojector needle-free injection system was easy to use for enfuvirtide administration and was associated with a decreased severity of ISR. Plasma enfuvirtide levels pre-dose and 1 h post-dose were comparable when injecting with standard needles or the Biojector.

Clinical Trial Result Information

Protocol number ML19235 (T20-405)

Title of Study An open-label, randomized, crossover study in HIV-positive subjects to determine and compare the single-dose pharmacokinetics of enfuvirtide (Fuzeon) after a single 90 mg sc administration with the Biojector 2000 Needle-Free Injection System and a 27G ½-inch (12.7 mm) needle/syringe

Sponsor Hoffmann-La Roche Inc; Trimeris Inc.

Company division Pharmaceutical

Product name Fuzeon

Generic name enfuvirtide

Therapeutic area HIV infection

Clinical study summary This was an open-label, randomized, 2-period, crossover, single-center study of the pharmacokinetics (PK), safety, and tolerability of enfuvirtide (Fuzeon) in HIV-positive patients involving 2 single-dose treatments using 2 different injection devices, with a 7-day washout phase between treatments.

Study center(s) 1 center in the United States.

Phase of development IV

Objectives

Primary: To determine the relative bioavailability of Fuzeon after a single sc 90 mg (1.0 mL) administration using 2 different injection devices: the B2000 Needle-Free Injection System and a 27G ½-inch (12.7 mm) needle/syringe.

Secondary: To compare the safety and tolerability of single doses of the 2 injection devices.

Methodology

Subject screening took place 7 to 30 days prior to the first dose of Fuzeon. Patients were scheduled to receive the following treatments: Treatment A: a single dose of 90mg (1.0mL) Fuzeon, delivered subcutaneously using a 27 gauge ½ inch (12.7mm) needle/syringe (Reference Treatment) Treatment B: a single dose of 90mg (1.0mL) Fuzeon, delivered by one 1.0mL subcutaneous injection, using needle-free Biojector ® 2000 injection system and No. 2 needle-free syringe (Test Treatment). Subjects received the 2 treatments according to a balanced randomization sequence. Each dose was administered as a single subcutaneous injection into the abdomen. A 1 week washout interval occurred between the two treatment periods.

Number of patients (planned/analyzed) 27

Diagnosis and main criteria for inclusion

HIV-1 infected adult patients who were treatment-naïve or patients who were on stabilized antiretroviral therapy (ARV) with HIV-1 viral loads <1000 copies/mL for 3 months prior to screening and at screening.

Test product, dose and mode of administration or test procedure

A single sc dose of 90mg (1.0mL) Fuzeon using a Biojector 2000 Needle-Free Injection System (B2000)

Duration of treatment

2 single doses, 7 days apart.

Reference therapy, dose and mode of administration or reference procedure

A single sc dose of 90 mg (1.0 mL) Fuzeon using a 27G ½-inch (12.7 mm) needle/syringe.

Criteria for evaluation (efficacy, safety)

Single-dose PK parameters, determined by noncompartmental methods for each treatment, included: C_{max} , t_{max} , AUC_{0-t} , and $AUC_{0-\infty}$. Ratios of C_{max} , AUC_{0-t} , and $AUC_{0-\infty}$ served as criteria for bioequivalence determination.

Safety: (1) Incidence of AEs, SAEs, and graded laboratory toxicities; (2) Specific signs and symptoms associated with local ISRs, including pain/discomfort during and following injection. Fuzeon tolerability analyses were based on assessments of clinical adverse events (including clinically significant laboratory abnormalities, graded laboratory toxicities, and local ISRs) leading to discontinuation from the study. A brief questionnaire was administered to patients at the end of the trial to determine their perception and preference regarding injection with the needle/syringe and B2000.

Statistical methods

All PK parameters were analyzed using a 2-way analysis of variance model (ANOVA). The primary analysis was based on logarithmic transformations of PK parameters. The model included sequence, period, and treatment as fixed effects, and subject within sequence as a random effect. The 90% confidence interval (CI) for the ratio of least squares means between test and reference treatment, derived from the ANOVA model, was used to assess bioequivalence. The two treatments were considered bioequivalent if the 90% CI for the ratios of log-transformed area under the serum concentration-time curve (AUC), AUC_{0-t} .

AUC $0-\infty$, and C_{\max} between treatments were within 80%-125%. Adverse events, (AEs), selected clinical safety laboratory test results, vital signs, physical examination findings, and local injection-site reactions (ISRs) were summarized.

Summary (efficacy, safety, other results) PK

Similar values for all calculated PK parameters were achieved between the 27G needle and B2000. A total of 26 patients had plasma PK data from both devices and served as the basis for the analysis of bioequivalence. Results of ANOVA bioequivalence testing indicated that the ratio of geometric least squares means of B2000 to 27G needle for log-transformed values of both AUC $0-\infty$ and AUC $0-\tau$ were 0.99 with a 90% CI (93%, 105%), within the equivalence region (80%–125%). The ratio of geometric least squares means of B2000 to 27G needle for log-transformed values of C_{\max} was 0.95 with a 90% CI (84%, 109%), which was also within the equivalence region (80%–125%). Thus, the 2 devices were bioequivalent based on the transformed values of AUC $0-\infty$, AUC $0-\tau$, and C_{\max} . Although not defined as part of the bioequivalence criteria in the analysis plan, the ratio for the plasma concentration of enfuvirtide at 12 hours post-dose (C_{12}) for the 27G needle and the B2000 was also determined. The ratio of geometric least squares means of B2000 to 27G needle for log-transformed values of C_{12} was 0.97 with a 90% CI (86%, 109%). Thus, both devices were also bioequivalent based on C_{12} . The AUCs for the devices were nearly identical.

Safety

All AEs were considered possibly related to Fuzeon by the investigator. Excluding ISRs, a total of 3 patients and 4 patients experienced AEs following injection of Fuzeon with the 27G needle and B2000, respectively. The only AE occurring in >1 patient was headache, occurring in 2 patients during the B2000 period. AEs in other body systems were experienced by single patients only. There was 1 drug-related serious adverse event (Grade 4 absolute neutrophil count [ANC]), noted during the follow-up period of the trial in a patient who had neutropenia on study entry. All treatment-emergent laboratory abnormalities (15 patients), were of Grade 1 severity, with the exception of the patient who experienced the Grade 4 ANC.

Injection Events and Local ISRs

No injection malfunctions or injection anomalies (ie, wet injections, partial dose delivered, leak-back etc) were noted with any injection for either device. The majority of patients reported no pain/discomfort during the injection for either the 27G needle (24/26) or the B2000 (22/27). During the B2000 period, all pain/discomfort experienced was reported as “mild tenderness at injection site” (14.8%, Grade 1), except for 1 patient during the B2000 period, who reported “moderate pain without limitation of usual activities” (Grade 2). In general, the majority of ISRs reported during the trial were mild and infrequent with both injection devices. No severity greater than Grade 2 was noted for any sign/symptom with either device.

Conclusions

Bioequivalence was achieved between the B2000 and 27G ½-inch needle for AUC_{0-∞}, AUC_{0-T}, C_{max}, and C₁₂. There were no clinically significant local ISRs for the B2000 or 27G needle. There was a comparable safety profile between the B2000 and 27G needle. Patients had a favorable overall opinion of the B2000 device, which constitutes a suitable alternative for sc delivery of Fuzeon.

Publications (references, if available)

True AL, Zhang Y, Chiu YY et al. Needle-free administration of enfuvirtide with Biojector TM 2000 (B2000) demonstrates pharmacokinetic bioequivalence to a standard needle administration. Proceedings DART 2004 (7th International Congress on Drug Therapy in HIV Infection)

Date of report 4/11/2005

Protocol number ML18596

Title of Study A randomized, open-label, two-way, crossover study to assess the tolerability of the B2000 needle-free injection device (NFID) for administration of enfuvirtide (ENF).

Sponsor Roche Laboratories Inc. and Trimeris Inc.

Company division Pharmaceutical

Product name Fuzeon

Generic name enfuvirtide

Therapeutic area HIV infection

Clinical study summary

This was an open-label, blinded injection site reaction (ISR) evaluator, randomized two period (28 days each) crossover trial evaluating the B2000 needle-free injection device and a standard 27G ½" needle/syringe for administration of Fuzeon (enfuvirtide).

Study center(s) 12 centers in the United States.

Phase of development IV

Objectives

Primary : To evaluate the tolerability of the B2000 NFID based on signs and symptoms associated with any Fuzeon injection. The primary endpoint is Painful Nodules/Induration (composite endpoint of grade 1-3 ongoing pain and either (a) grade 3-4 induration (≥25 mm) or (b) grade 2-4 nodules/cysts (>20 mm) when using the B2000 NFID, in comparison to a standard 27G ½" needle/syringe (NS), during chronic self-administration).

Secondary : To determine the adherence, overall satisfaction, and preference for chronic

self-administration of Fuzeon between the B2000 NFID and a 27G ½" needle/syringe. To determine and compare the pre-dose steady-state C_{trough} levels of Fuzeon following chronic self-administration with the B2000 NFID vs. the 27G ½" needle/syringe for abdominal injections.

Methodology

During the 28-day evaluation period, subjects self-administered 56 injections with each assigned device. For consistency, it was recommended that subject give injections while in a similar body position (always sitting, always standing, etc). Any ISR present at the in-clinic evaluations (ongoing ISR) were evaluated and recorded by severity grade and body location by a treatment-blinded clinician. Four pre-AM blood samples per dosing period were drawn for the determination of C_{trough} .

Number of patients (planned/analyzed)

58 randomized. 48 in safety analysis. 28 in ISR analysis.

Diagnosis and main criteria for inclusion

Fuzeon-naïve HIV-1 infected adults (≥ 18) with no active untreated opportunistic infections.

Test product, dose and mode of administration or test procedure

Fuzeon 90 mg/mL sc bid with either a 27G ½" needle/syringe (NS) or Biojector 2000 (B2000) device for 28 days each.

Duration of treatment 56 days.

Reference therapy, dose and mode of administration or reference procedure N/A

Criteria for evaluation (efficacy, safety)

Efficacy: No efficacy parameters were evaluated in this trial. **Pharmacodynamics:** No pharmacodynamic parameters were evaluated in this trial. **Pharmacokinetics:** Steady-state C_{trough} assessments only for abdominal injections with each device.

Safety: Treatment-emergent Adverse Events, AIDS-defining events, graded laboratory toxicities, and injection site reactions (ISR). **Subject preference/satisfaction:** After completing dosing periods with both devices, subjects were asked to state which device they preferred and with which they were more satisfied.

Statistical methods

Forty evaluable subjects treated with each device would allow estimation with 95% confidence of the difference in responses between devices of less than 15% (half-width of 95% CI), assuming an observed response rate of 45% for the incidence of subjects having the painful ISRs primary endpoint. Based on an expected binary endpoint of 45% with NS administration of Fuzeon, an assumed discordant pairs rate of 27%, and employing a 2-sided exact McNemar's test for paired binary data at a 5% significance level, 40 subjects would allow for detection of a statistically significant difference of 23% with 80% probability.

Summary (efficacy, safety, other results)

Safety: Mean subject adherence was similar between the two devices (97.7% B2000 and 98.3% NS). A similar number of subjects experienced AEs on the B2000 (22/44) as compared to the needle/syringe (22/46). Four subjects experienced SAEs during this trial, 2 in the B2000 arm and 2 in the needle/syringe arm. None of the SAEs was considered related to Fuzeon. One SAE (hematoma) was considered related to the B2000 device but the subject elected to continue dosing with the B2000 for the remainder of the trial and thereafter. One subject withdrew from the trial due to an ISR experienced while dosing with the NS.

ISR results: A total of 40 patients were dosed with both devices. Of these, 12 patients from one site were excluded from the ISR analysis due to flawed ISR evaluations, leaving an ISR population of 28 patients. Across all injection locations, fewer subjects on the B2000 experienced Painful ISRs (31%) compared to those on the needle/syringe (59%, $p=0.004$). Fewer subjects experienced any Grade 2-4 ISR in the abdomen or the arm/thigh on the B2000 (68%) vs. NS (86%; $p=0.025$). Fewer subjects experienced any grade (G1-3) of ongoing abdominal pain/discomfort on the B2000 (75%) compared to those on the NS (96%; $p=0.014$). Fewer subjects experienced any grade (G1-3) ongoing pain/discomfort in all injection locations on the B2000 compared to the NS (79% B2000 vs. 96% NS; $p=0.025$). Fewer subjects experienced any grade of abdominal ecchymosis on the B2000 (36%) compared to the NS (61%; $p=0.020$). More subjects experienced G2-4 ecchymosis on the B2000 (29%) vs. NS (11%; $p=0.025$) in the arm/thigh with abdomen as an optional site. Fewer subjects experienced abdominal G2-3 pruritus on the B2000 (7%) than the NS (21%; $p=0.046$). A weighted overall ISR severity summary score was derived by totalling the severity grades for each individual sign/symptom, and dividing by the total number of individual ISRs present. Across all injection sites, the median weighted overall ISR severity summary score was lower on the B2000 (2.6, range 0.3-5.9) compared to the needle/syringe (3.6, range 0.4-7.9; $p=0.0183$).

Overall subject preference/satisfaction: 31 subjects (83.8%) preferred and were more satisfied with the B2000 for administration of Fuzeon compared to 6 subjects (16.2%) who preferred and were more satisfied with the needle/syringe.

Pharmacokinetics: The ratio of the LS means for C_{trough} between the two devices was 0.817 (B2000/27G NS), which fell within the 90% CI of 0.612, 1.092.

Conclusions

The B2000 constitutes a safe, viable and preferred option for the chronic self-administration of Fuzeon and may offer significant improvements in Painful ISRs, ongoing pain/discomfort, ecchymosis and pruritus in comparison to a standard needle/syringe.

Publications (references, if available)

Needle-free Administration Of Enfuvirtide Significantly Reduces Incidence Of Painful Injection Site Reactions: Results From A Single Blind, Randomized, Controlled Study. Abstract #1905b, 46th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), San Francisco, CA, USA, Sept 27-30, 2006.

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