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# Comparison of the Efficacy and Side Effects of IFN Beta 1–a (Rebif) and a Biosimilar Product (Recigen) in Patients with Multiple Sclerosis

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## Abstract

**Background:** Multiple Sclerosis, or MS, is a chronic demyelinating disorder of the central nervous system affecting over 400,000 people in the US and 2 million individuals worldwide. MS often results in severe disability. Unfortunately, the etiology of multiple sclerosis is unknown and there is no known cure for the disease, and treatments are modest at best. Although, many drugs were found and produced for the treatment of MS, such as Rebif, Avonex and etc, these drugs are often very expensive. Recigen, which is an Iranian biosimilar product, is the same as Rebif. In this study we compared the efficacy and side effects of Rebif and Recigen in the treatment of MS.

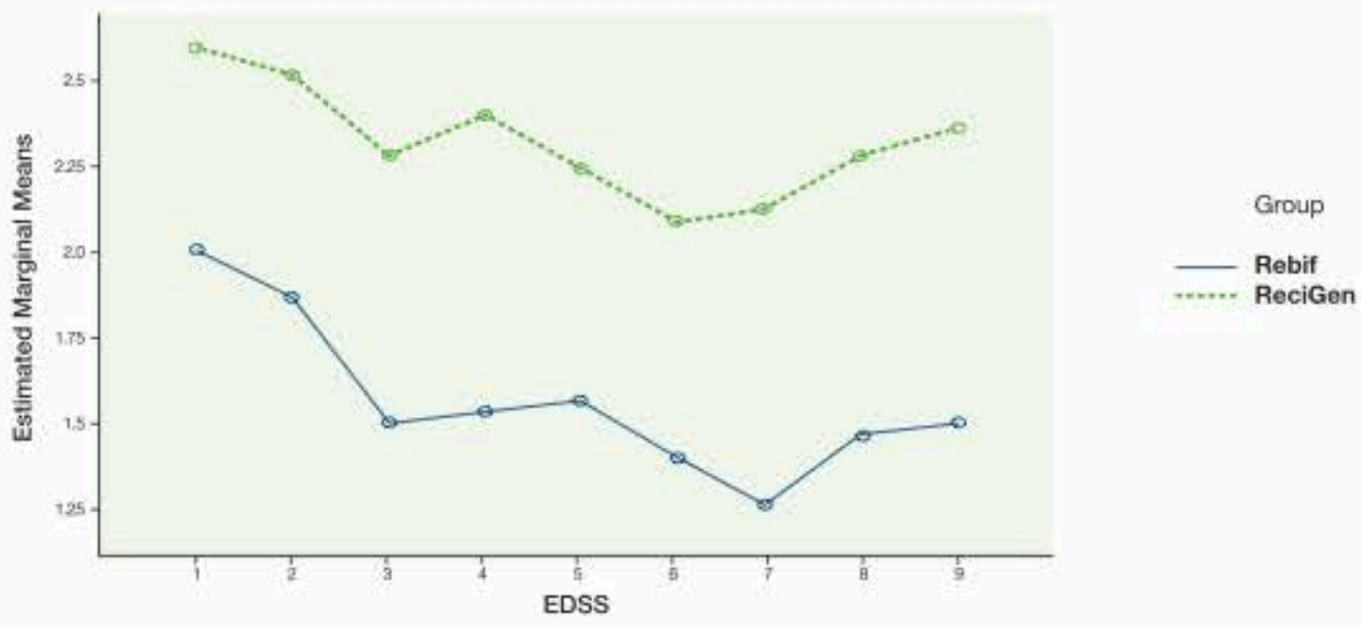
**Methods:** In a randomized clinical trial 44 patients with EDSS between 0-4 were enrolled and divided into two groups. Of these patients 36 were followed up to the end of the study. The first group was treated by Rebif and the second was treated by Recigen for 24 months. During the study, EDSS, relapses drug complications, active plaques and plaque volume were studied and recorded in a special form. Finally all data were analyzed by SPSS software. The chi-square, student's t-test and repeated measures ANOVA were used for data analysis.

**Findings:** According to the results of this study the trend of EDSS between two groups was the same, and there was no statistical difference between the two groups (P = 0.13). Moreover, no statistical difference was seen between the two groups in relapse number (P = 0.6). In addition, the plaque volume in both groups decreased, but there was no difference between the two groups.

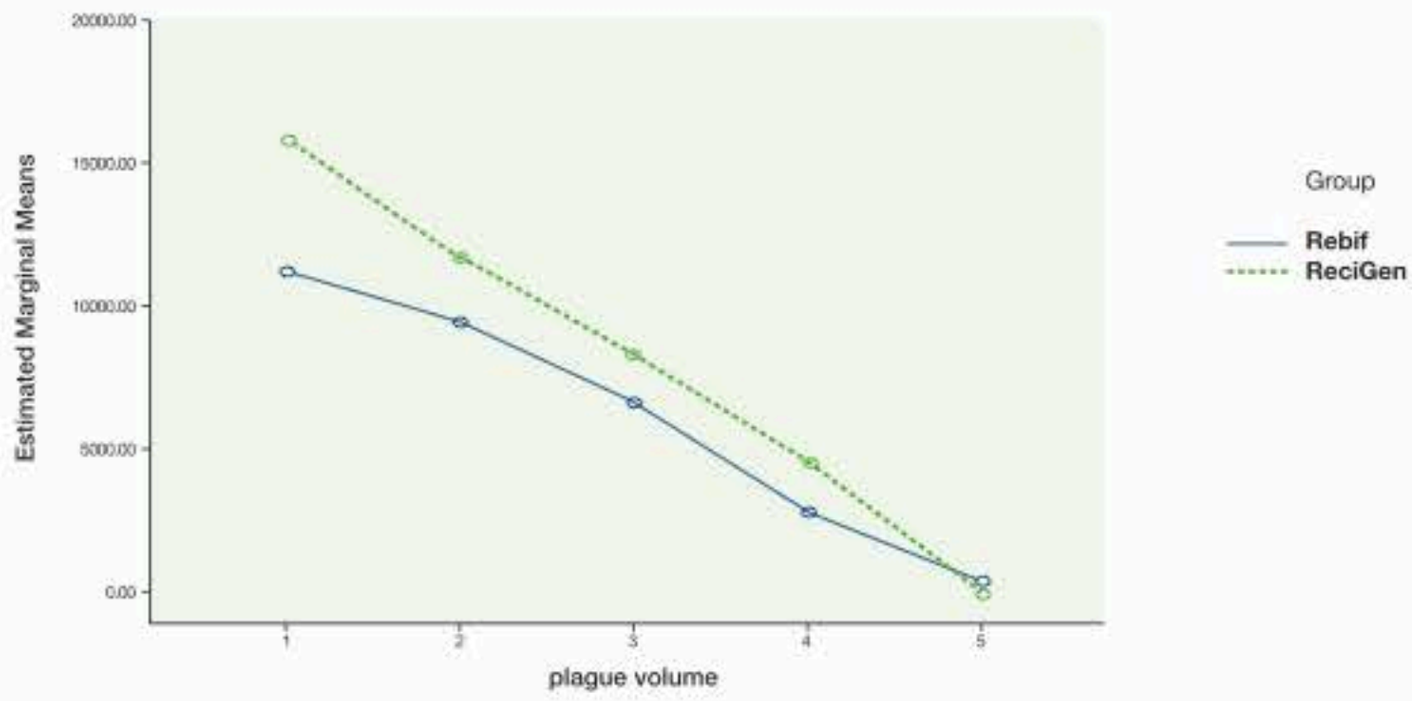
**Conclusion:** The results of this study showed that Recigen is as effective as rebif and has no significant side effects in comparison with Rebif.

**Keywords:** Multiple Sclerosis, Rebif, Recigen

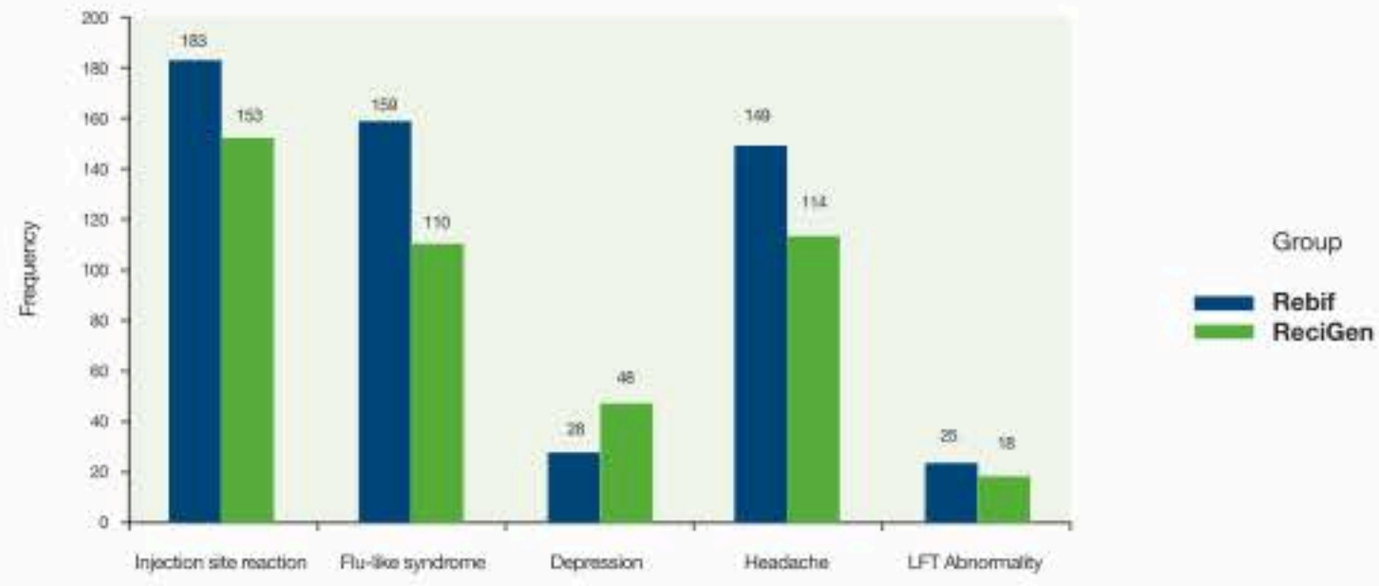
## EDSS changes during treatment period in two groups




## Changes in volume of demyelinated plaques during treatment period in two groups




## Frequency of each adverse effect in two groups



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## Safety

Recigen will not cure multiple sclerosis (MS) but it has been shown to decrease the number of flare-ups and slow the occurrence of some of the physical disability that is common in people with MS. The most common side effects of Recigen are injection-site reactions, flu-like symptoms, depression, abdominal pain, elevated liver enzymes, and blood abnormalities. Potential serious side effects include depression, suicidal ideation, suicide attempts, liver problems with the possibility of severe liver injury, allergic reactions and injection-site problems with a chance of infection or severe skin damage.

## Adverse Reactions

### >10%:

**Central nervous system:** Headache (58% to 70%), fatigue (33% to 41%), fever (20% to 28%), pain (23%), chills (19%), depression (18% to 25%), dizziness (14%)

**Gastrointestinal:** Nausea (23%), abdominal pain (8% to 22%)

**Genitourinary:** Urinary tract infection (17%)

**Hematologic:** Leukopenia (28% to 36%)

**Hepatic:** ALT increased (20% to 27%), AST increased (10% to 17%)

**Local:** Injection site reaction (3% to 92%)

**Neuromuscular & skeletal:** Myalgia (25% to 29%), back pain (23% to 25%), weakness (24%), skeletal pain (10% to 15%), rigors (6% to 13%)

**Ocular:** Vision abnormal (7% to 13%)

**Respiratory:** Sinusitis (14%), upper respiratory tract infection (14%)

**Miscellaneous:** Flu-like syndrome (49% to 59%), neutralizing antibodies (24%), lymphadenopathy (11% to 12%)

### 1% to 10%:

**Cardiovascular:** Chest pain (5% to 6%), vasodilation (2%)

**Central nervous system:** Migraine (5%), somnolence (4% to 5%), malaise (4% to 5%), seizure (1% to 5%)

**Dermatologic:** Erythematous rash (5% to 7%), maculopapular rash (4% to 5%), alopecia (4%), urticaria

**Endocrine & metabolic:** Thyroid disorder (4% to 6%)

**Gastrointestinal:** Xerostomia (1% to 5%), toothache (3%)

**Genitourinary:** Micturition frequency (2% to 7%), urinary incontinence (2% to 4%)

**Hematologic:** Thrombocytopenia (2% to 8%), anemia (3% to 5%)

**Hepatic:** Bilirubinemia (2% to 3%)

**Local**: Injection site pain (8%), injection site bruising (6%), injection site necrosis (1% to 3%), injection site inflammation

**Neuromuscular & skeletal:** Arthralgia (9%), hypertonia (6% to 7%), coordination abnormal (4% to 5%)

**Ocular:** Eye disorder (4%), xerophthalmia (1% to 3%)

**Respiratory:** Bronchitis (8%)

**Miscellaneous:** Infection (7%)

### <1%:

**(Limited to important and life-threatening):** Anaphylaxis, autoimmune hepatitis, cardiomyopathy, CHF, hepatic failure, hepatitis, hyper-/hypothyroidism, idiopathic thrombocytopenia, injection site abscess/cellulitis, menorrhagia, metrorrhagia, pancytopenia, psychiatric disorders (new or worsening; including suicidal ideation), vesicular rash

## Contraindications

Hypersensitivity to natural or recombinant interferons, human albumin, or any other component of the formulation

## Warnings/Precautions

### Concerns related to adverse effects:

- **Anaphylaxis/hypersensitivity reactions:** Allergic reactions, including anaphylaxis, have been reported.
- **Autoimmune disorders:** Autoimmune disorders including idiopathic thrombocytopenia, hyper- and hypothyroidism and rarely autoimmune hepatitis have been reported.
- **Bone marrow suppression:** Pancytopenia (rare) and thrombocytopenia have been reported; use with caution in patients with bone marrow suppression.
- **Flu-like symptoms:** Associated with a high incidence of flu-like adverse effects; use of analgesics and/or antipyretics on treatment days may be helpful.

- **Hepatic effects:** Rare cases of severe hepatic injury, including hepatic failure, have been reported in patients receiving interferon beta-1a; risk may be increased by ethanol use or concurrent therapy with hepatotoxic drugs. Treatment should be suspended if jaundice or symptoms of hepatic dysfunction occur. Some reports indicate symptoms began after 1-6 months of treatment. Transaminase elevations may be asymptomatic, so monitoring is important.
- **Neuropsychiatric disorders:** Interferons have been associated with severe psychiatric adverse events (psychosis, mania, depression, suicidal behavior/ideation) in patients with and without previous psychiatric symptoms, avoid use in severe psychiatric disorders and use caution in patients with a history of depression; patients exhibiting symptoms of depression should be closely monitored and discontinuation of therapy should be considered.

### Disease-related concerns

- **Cardiovascular disease:** Use with caution in patients with pre-existing cardiovascular disease, including angina, HF, and/or arrythmia. Rare cases of new-onset cardiomyopathy and/or HF have been reported.
- **Hepatic impairment:** Use with caution in patients with hepatic impairment or in those who abuse alcohol. Dosage adjustment may be necessary.
- **Seizure disorder:** Use with caution in patients with a history of seizure disorder.

### Special populations

- **Chronic progressive MS:** Safety and efficacy have not been established for this use.
- **Pediatrics:** Safety and efficacy have not been established in children.
- **Geriatric:** Clinical studies did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently than younger subjects.
- In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

### Dosage form specific issues

- **Albumin:** Some formulations contain albumin, which may carry a remote risk of transmitting Creutzfeldt-Jakob or other viral diseases. Interferon beta-1a is contraindicated in albumin-sensitive patients.

### Drug Interactions

- **Theophylline Derivatives:** Interferons may decrease the metabolism of Theophylline Derivatives. Monitor therapy
- **Zidovudine:** Interferons may enhance the adverse/toxic effect of Zidovudine. Interferons may decrease the metabolism of Zidovudine. Monitor therapy
- Due to its potential to cause neutropenia and lymphopenia, proper monitoring of patients is required if ReciGen is given in combination with myelosuppressive agents.
- The potential for hepatic injury should be considered when ReciGen is used in combination with other products associated with hepatic injury, or when new agents are added to the regimen of patients already on ReciGen.

### Pregnancy Implications

There are no adequate and well-controlled studies in pregnant women. Consideration should be given to discontinue treatment if a woman becomes pregnant, or plans to become pregnant during therapy. A dose-related abortifacient activity was reported in Rhesus monkeys.

### Lactation

Excretion in breast milk unknown. Use not recommended.

### Breast-Feeding Considerations

Its use has not been evaluated during lactation, a decision should be made to either discontinue breast-feeding or discontinue the drug.

### Monitoring Parameters

Thyroid function tests, CBC with differential, transaminase levels, symptoms of autoimmune disorders, signs/symptoms of psychiatric disorder (including depression and/or suicidal ideation), signs/symptoms of new onset/worsening cardiovascular disease.

CBC and liver function testing at 1, 3 and 6 months, then periodically thereafter. Thyroid function every 6 months (in patients with pre-existing abnormalities and/or clinical indications).

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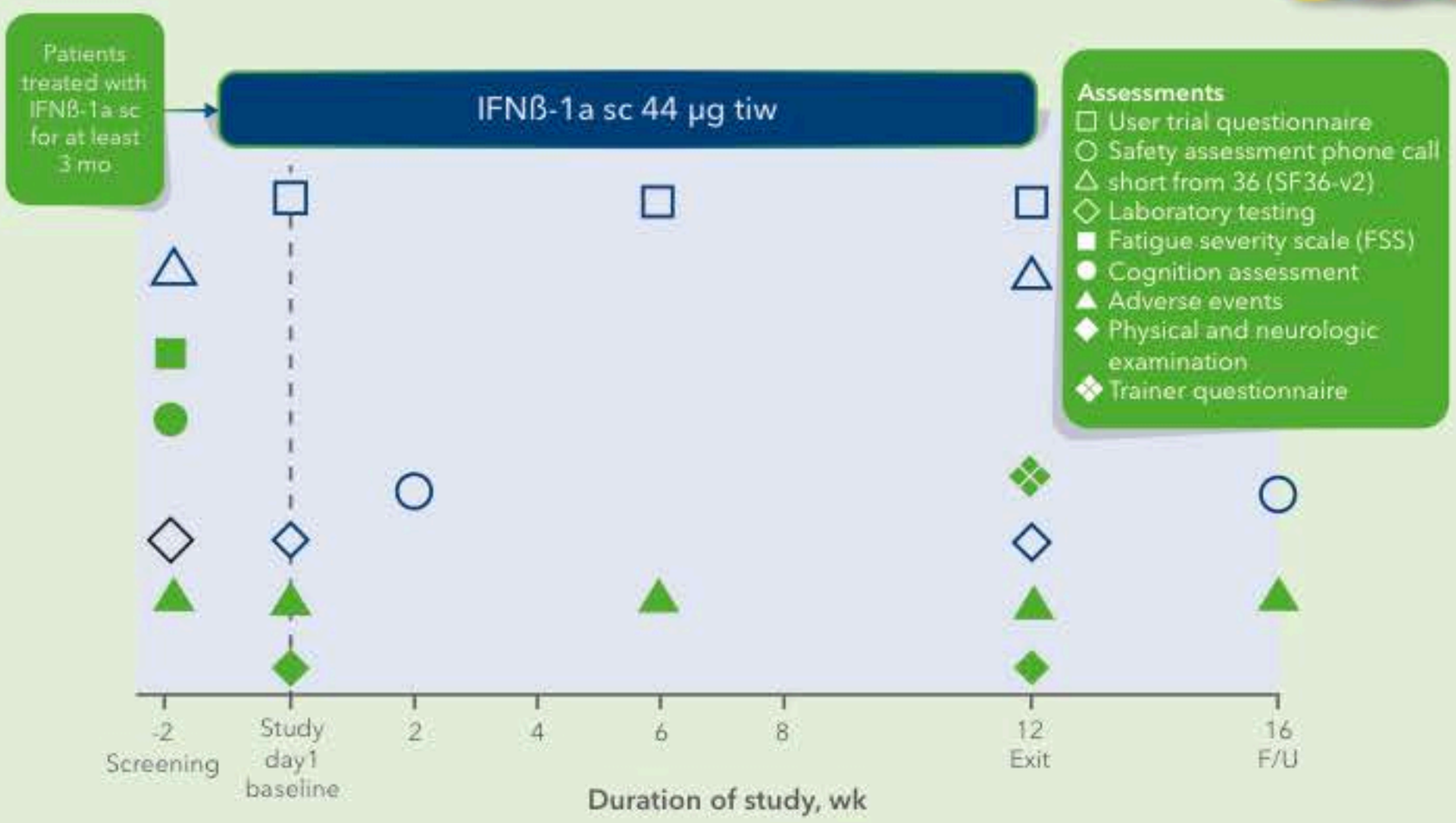


Figure 1. Schedule of study assessments.

- A 12-week, Phase IIIb, open-label, single-arm, multicenter trial conducted at 12 sites in the United States. Patients enrolled in the trial were treated for MS with IFNb-1a 44 µg sc tiw therapy using the single-use autoinjector for 12 weeks.
- Patients completed a 32-item user trial questionnaire. The questionnaire was administered at study day 1 and at weeks 6 and 12.
- Primary endpoint: The proportion of patients rating the autoinjector as easy or very easy to use at week 12.
- Secondary endpoints: functional reliability and patient satisfaction with device attributes and convenience.

# Autoinjector: Improved Compliance & Higher Safety

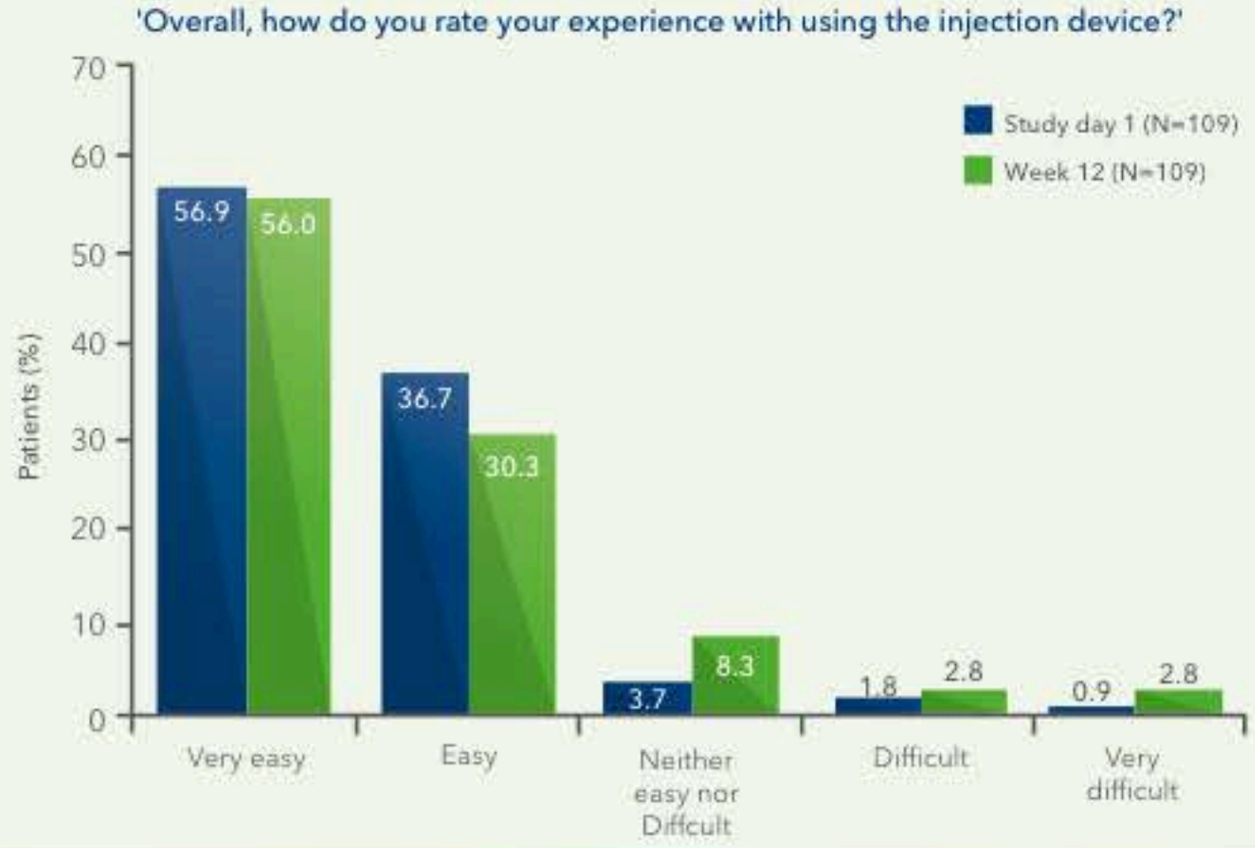


**Figure 2.** Primary endpoint: patient perception of the ease of the use of the single-use autoinjector at study day 1 and week 12 from the User Trial Questionnaire.

- Of 109 patients, 94 (86% (95% CI, 80% -- 93%)) reported at week 12 that the single-use autoinjector was easy or very easy to use.

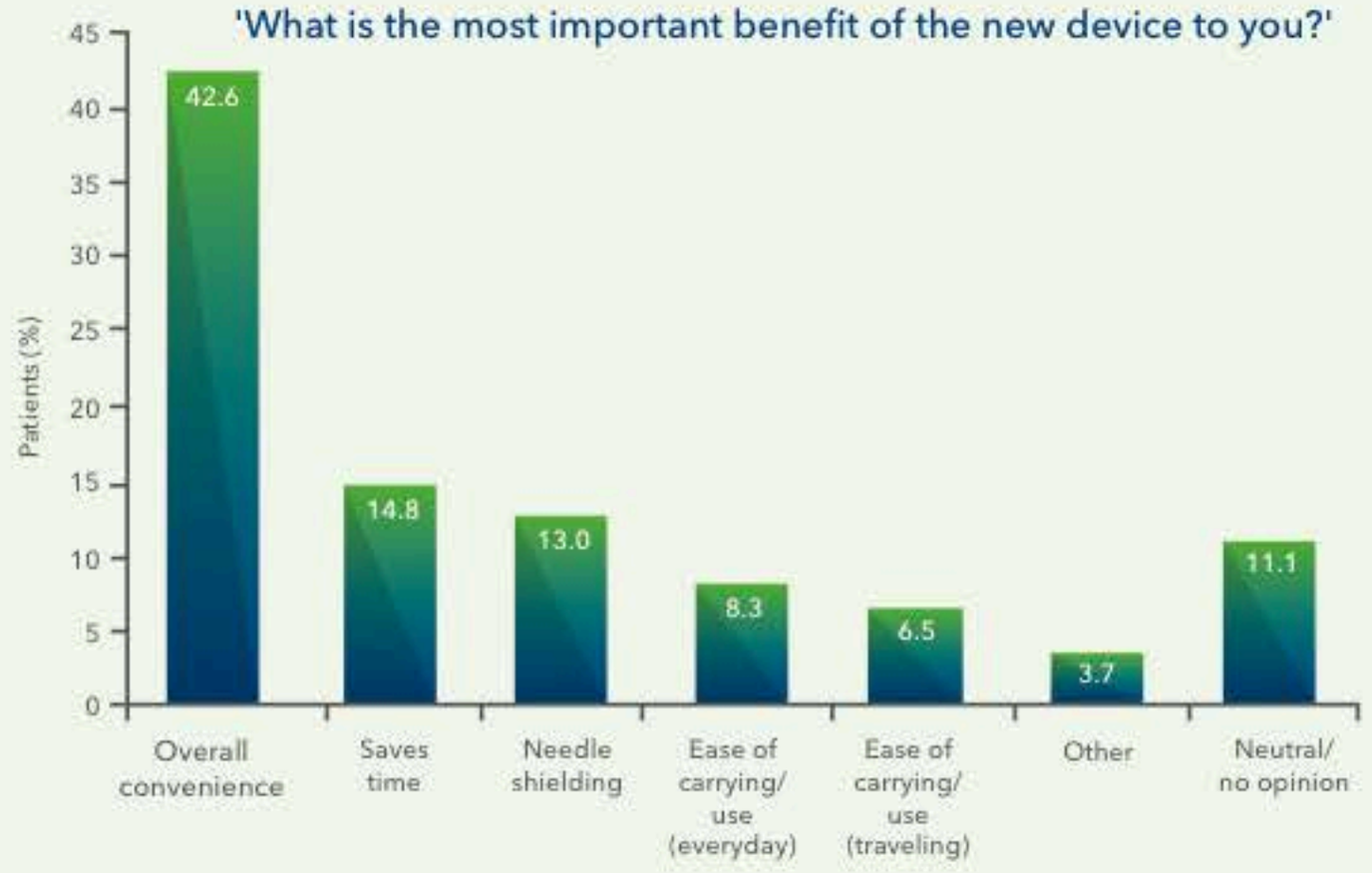


**Figure 3.** Patient evaluation of most important benefits of the device at week 12 from the User Trial Questionnaire.

- Data at 12 weeks indicated that the single-use autoinjector was functionally reliable, with 96% (95% CI, 93% -- 100%) patients reporting that they were often or always able to administer the full injection with the new device.
- According to 83% (95% CI, 77% -- 90%) patients, the device simplified injections.
- Overall convenience, ability to save time and needle shielding were the highest rated aspects of the single-use autoinjector.

**Reference:**
Wray S, Armstrong R, Herrman C, Calkwood J, Cascione M, Watsky E et al. Results from the single-use autoinjector for self-administration of subcutaneous interferon beta-1a in patients with relapsing multiple sclerosis (MOSAIC) study. Expert Opin Drug Deliv. 2011;8(12):1543-53.

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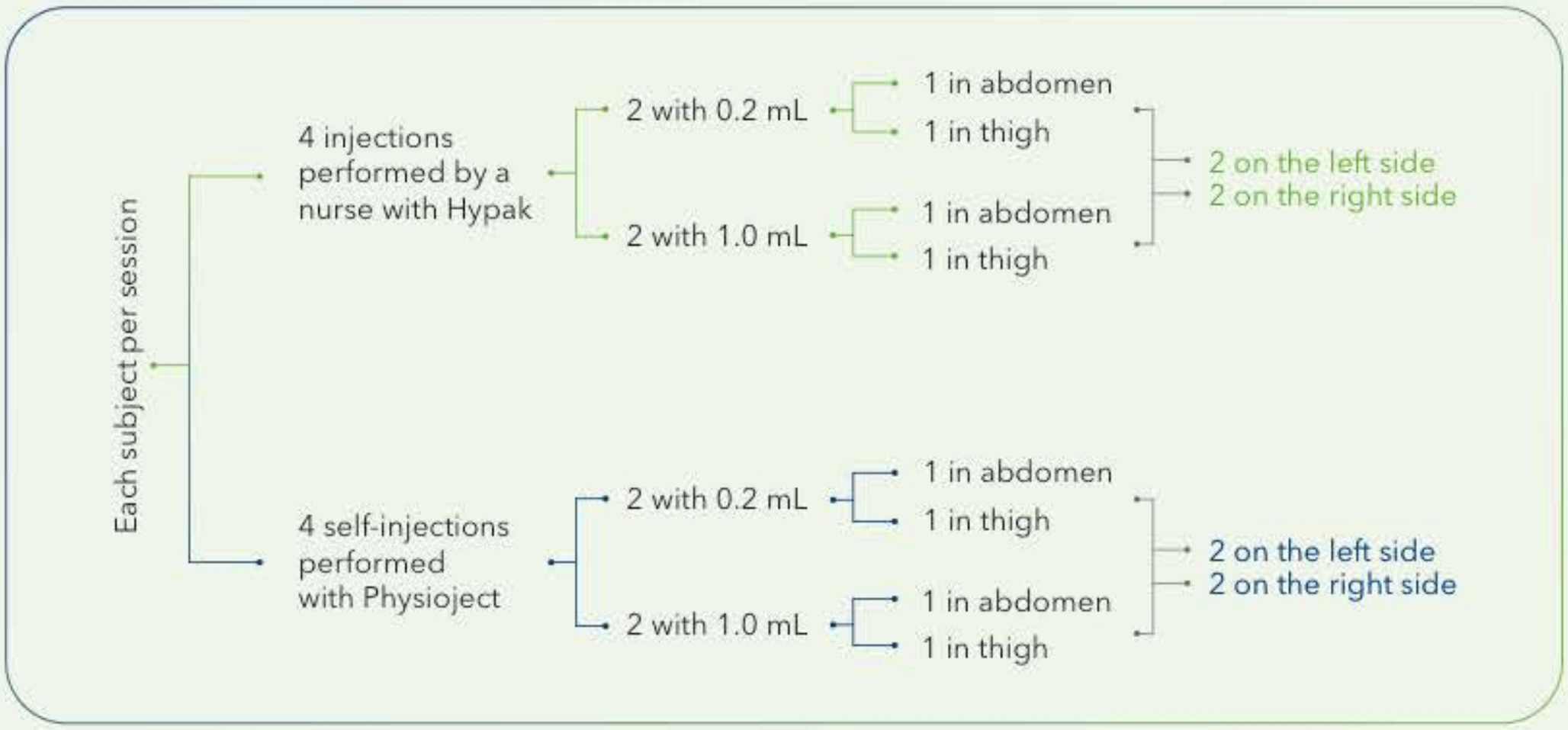


Figure 1. Study Design

- A randomized, single-center, crossover study comparing SC self-injection using an autoinjector with SC nurse-administered injection using a syringe.
- Each subject came for three separate sessions of eight injections. The order of injections was balanced across all subjects in terms of the system, volume, and injection site, and subjects were randomly assigned to a prespecified order of injection (Figure 1).
- Pain measured by a VAS (Visual Analog Scale) immediately after each of the 960 injections.
- Primary Endpoint: Fluid leakage and injected volume, gravimetric method
- Secondary Endpoint: Perceived pain, 100 mm VAS

# Autoinjector: Lower Pain, Higher Acceptance

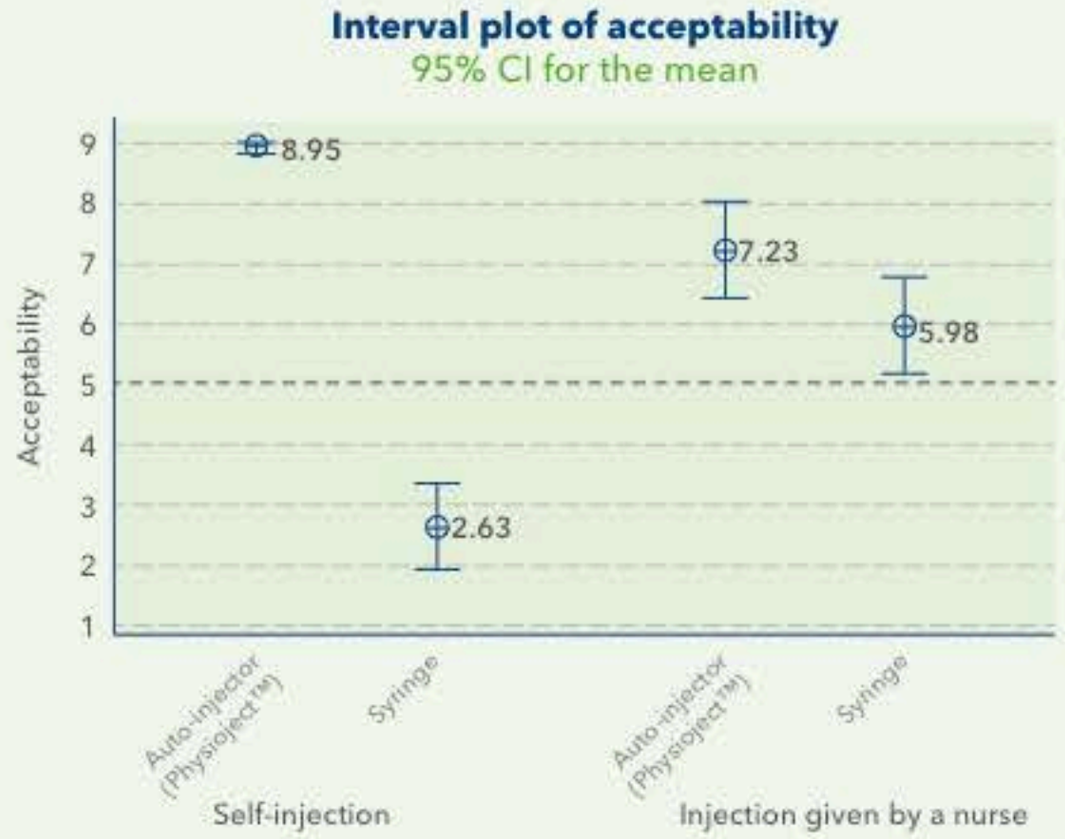


Figure 2. Device acceptability score for four injection scenarios (mean and %95 confidence interval).

- All subjects selected self-injection with the autoinjector as the preferred injection system at the end of the study.

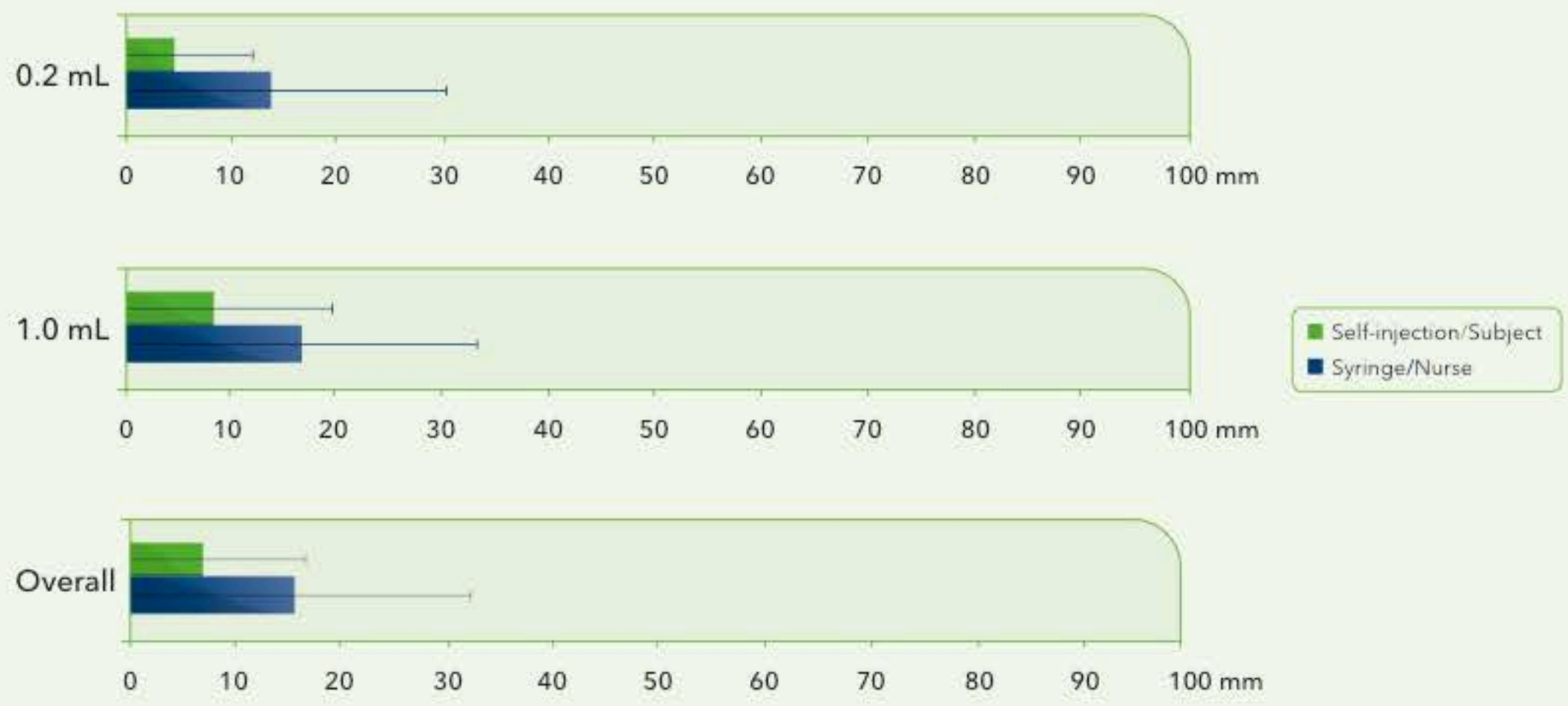


Figure 3. Subjects reported significantly less pain when injections were self-administered by the autoinjector than when given by nurses with the syringe ($P < 0.0001$), and with an injection of 0.2 mL rather than 1.0 mL ($P = 0.0003$).

- There were no significant differences in mean fluid leakage, injected volumes and fluid depot location in the hypodermis after injection between the autoinjector device and PFS.
- Skin reactions were not significantly different between two groups; however, Local edema was more frequent with injections by nurses (p value <0.0001).

**Reference:**
Berteau C, Schwarzenbach F, Donazzolo Y, Latreille M, Berube J, Abry H, et al. Evaluation of performance, safety, subject acceptance, and compliance of a disposable autoinjector for subcutaneous injections in healthy volunteers. Patient Prefer Adherence. 2010;4:379-88.

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