Expert Opinion

Results from the single-use autoinjector for self-administration of subcutaneous interferon beta-1a in patients with relapsing multiple sclerosis (MOSAIC) study

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Background: Patients with multiple sclerosis (MS) often receive long-term injectable therapy, and difficulties associated with self-injection can affect treatment adherence and efficacy.
Objective: The objective of this study was to evaluate an investigational, ready-to-use, single-use autoinjector for self-injection of subcutaneous (sc) interferon beta-1a (IFNβ-1a).
Methods: In this multicenter, open-label, single-arm study, patients with relapsing MS who were receiving IFNβ-1a sc 44 μg three times weekly for ≥ 12 weeks continued therapy using a single-use autoinjector and completed a user trial questionnaire at baseline and weeks 6 and 12. The primary endpoint was the proportion of patients rating the autoinjector as easy or very easy to use at week 12.
Results: At 12 weeks, 86% of 109 patients included in the intent-to-treat population rated the autoinjector easy or very easy to use (95% confidence interval, 80% - 93%), and the most important perceived benefit was its overall convenience. The majority (74%) of patients reported the device as somewhat or extremely convenient to use, and most (83%) agreed or strongly agreed that the device made injections simple.
Conclusion: The single-use autoinjector was well received and supported by favorable ratings for simplified injections and convenience. The results suggest that the device may improve overall injection experience in patients with relapsing MS.

Keywords: medication adherence, multiple sclerosis, subcutaneous injections

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1. Introduction

Multiple sclerosis (MS) is a chronic condition that can be effectively managed with disease-modifying injectable therapies. Unfortunately, treatment adherence in patients with chronic conditions tends to be low, with the World Health Organization previously reporting an average adherence rate of 50% among patients in developed countries [1]. Barriers to adherence may include forgetfulness, deliberate omission of doses, and emotional or other factors typically under the patient's control [2]. Other variables that could affect adherence may be directly related to the treatment regimen, such as complexity of the regimen or interference with

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patient lifestyle. In MS, suboptimal adherence has been attributed to such factors as the inconvenience of frequent injections or patient discomfort [3].

An important component of optimizing adherence to and ultimately achieving the full benefit of therapy in any chronic illness involves increasing the convenience of care. In illnesses such as diabetes or MS with management often requiring the repeated administration of injectable therapies, this goal may be achieved with the use of devices designed to aid the patient with self-injection [4-6]. To that end, a ready-to-use, single-use autoinjector has been developed for patients with relapsing MS taking interferon beta (IFNβ)-1a in subcutaneous (sc) mode three times weekly (tiw) in an attempt to simplify injections and enhance patient satisfaction. The device is designed to improve patient convenience and ease of use. The Multicenter, Open-label, Single-use Autoinjector Convenience (MOSAIC) study evaluated the autoinjector with respect to ease of use, patient satisfaction and acceptability, convenience and functional reliability.

2. Methods

2.1 Study design

This was 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 IFNβ-1a 44 μg sc tiw therapy using the single-use autoinjector for 12 weeks.

2.2 Patient selection

Male and female patients were eligible for inclusion in the study if they were aged 18 – 65 years and diagnosed with relapsing MS as defined by McDonald criteria (revised, 2005) [7,8]. At the time of screening, patients were required to have been receiving IFNβ-1a 44 μg sc tiw via manual injection with a prefilled syringe or the Rebiject II autoinjector (a reusable autoinjector with an adjustable injection-depth feature) for at least 12 weeks, be capable of self-injection and be willing to comply with the study procedures for the duration of the trial. Women of childbearing potential had to have a negative pregnancy test at baseline and at week 12. All patients had to provide a signed informed consent agreement and had to sign a Health Insurance Portability and Accountability Act authorization before entering the study.

Patients were excluded if they had

- used any other injectable medication (other than IFNβ-1a 44 μg sc tiw) on a regular basis within 1 week of screening or throughout the duration of the trial,
- received any MS therapy other than IFNβ-1a 44 μg sc tiw within 12 weeks of screening or at any time during the trial,
- demonstrated abnormal liver function (defined by levels of alanine aminotransferase, alkaline phosphatase or total bilirubin that were > 2.5 times the upper limits of normal),
- displayed inadequate bone marrow reserve (defined by total white blood cell count < 3.0×10^9/L, platelets < 75×10^9/L, hemoglobin < 100 g/L),
- had a medical history of substance abuse or uncontrolled seizures,
- showed presence of complete transverse myelitis, bilateral optic neuritis, thyroid dysfunction, moderate to severe renal impairment, serious or acute cardiac disease or any medical or psychiatric conditions or visual or cognitive impairments that, in the opinion of the investigator, would preclude study participation,
- participated in another clinical trial within 30 days of screening and
- displayed a known allergy or hypersensitivity to IFNβ drugs or any of the excipients.

2.3 Device and administration

The ready-to-use autoinjector is intended for single-use administration only, and each syringe contains IFNβ-1a 44 μg. Before injecting, patients were advised to allow the device to warm to room temperature. It was recommended that patients examine the contents of the syringe through the transparent plastic housing, checking for cloudiness, discoloration or whether it contained particles, and to check the housing for structural integrity. Patients were then instructed to hold the device by the injector body, remove the needle cap, and check that the black needle shield was inside the cap. After holding the autoinjector in the palm of their hand with their thumb above the injector button, and placing the needle end flat against their skin, the device was ready to inject.

The device was to be used to administer IFNβ-1a 44 μg sc tiw for 12 weeks. No dose titration was necessary because enrolled patients had been receiving the study drug for at least 12 weeks before study entry. Patients received training on the use of the autoinjector on study day 1. The first self-injection was performed under trainer supervision on study day 1.

2.4 Patient assessments

The complete schedule of assessments is shown in **Figure 1**. At screening, patients were asked to complete the Fatigue Severity Scale (FSS), the Short Form-36 Version 2 (SF-36v2™) Health Survey, and a computerized cognition assessment battery [9,10]. The SF-36v2 Health Survey was also repeated at week 12.

The FSS [11] is a nine-statement patient self-rating questionnaire for the level of fatigue on a 7-point scale (1 = strong disagreement, 7 = strong agreement). Average scores ≥ 5.8 were considered abnormal and associated with MS-related fatigue. The SF-36v2 Health Survey [12] consists of 36 patient-rating questions that measure functional health and well-being over eight health domains (physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional and mental health scales). The

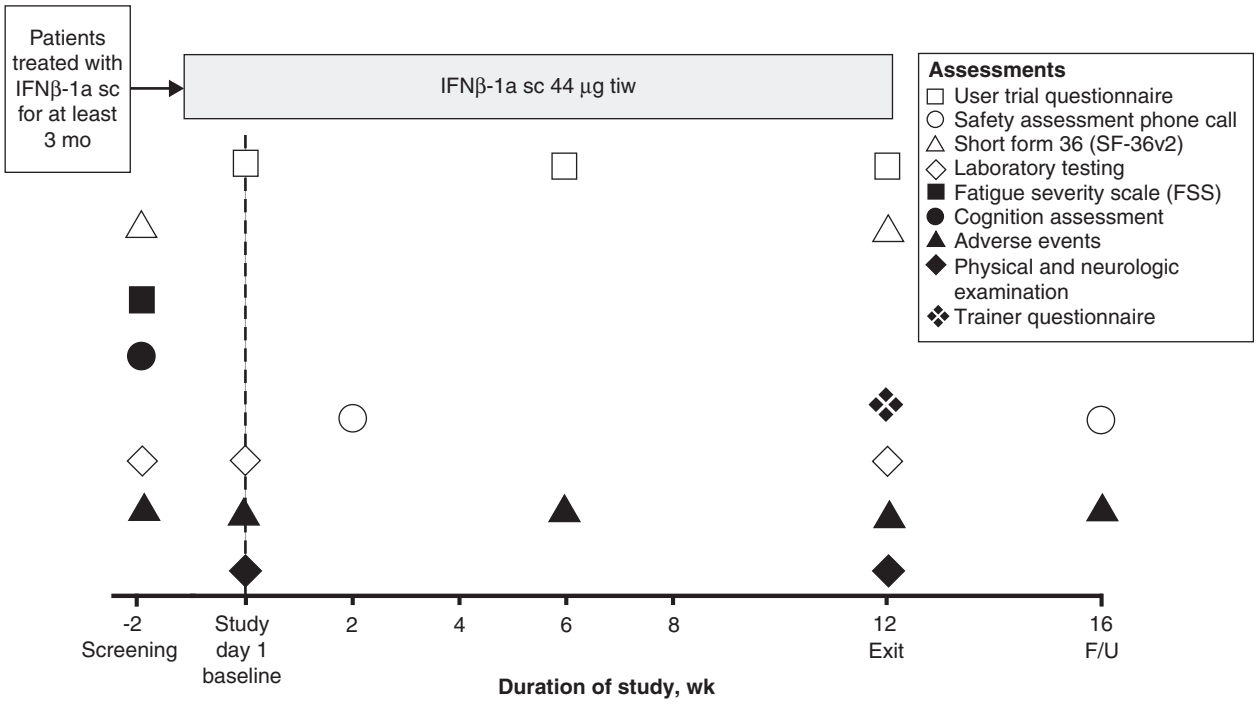

Figure 1. Schedule of study assessments.
F/U: Follow-up; IFNβ: Interferon beta; sc: Subcutaneous; tiw: 3 times weekly.

cognition assessment (Neurotrax Mindstreams®; Fresh Meadows, NY) battery consists of interactive computerized tests that measure performance in several areas including memory, executive function, attention, verbal function and information processing. This computerized neuropsychological assessment of cognitive function has been previously validated [9,10]. Standardized index scores obtained with the cognitive battery were categorized as "normal," "probable normal," "probable abnormal" or "abnormal," with the latter three interpreted as "non-normal." Neurologic assessments were performed at baseline and week 12 and included 72 items related to mental status, cranial nerves, muscle tone, muscle strength, reflexes, sensory exam, coordination and gait. Status measures of overall tone, strength and reflexes were limited to abnormalities in the hand, fingers, arms and shoulders of the dominant hand. Findings of the nondominant upper extremity or the lower extremities were excluded, owing to the likely contribution of abnormalities in the dominant upper extremity to problems in using the device. Neurologic assessment was considered abnormal if the evaluator determined a deficit in ≥ 1 of the 72 items at study day 1.

Patients completed a 32-item user trial questionnaire designed to survey the ease of use, functional reliability, and patient satisfaction and acceptability of the single-use autoinjector. The questionnaire was administered at study day 1 and at weeks 6 and 12. Responses to 25 of the questions were coded on a scale that ranged from 2 (eg, strongly agree, very easy, always or extremely satisfied) to -2 (eg, strongly disagree, very difficult, never or extremely dissatisfied). A question on the most important benefit of the device had seven possible listed answers from which to choose. The likelihood and extent of future use were queried based on two questions that were binary (yes and no). There were also four questions that were asked only once at week 12/exit visit. They included one question on reliability of the device with a five-point response scale ranged from extremely reliable to extremely unreliable, two questions on activities of daily living on a scale of 0 (no difficulty at all) to 3 (a great deal of difficulty) and one question that provided choices for the previous injection device used.

At week 12, study-site personnel responsible for training patients on the use of the device completed a questionnaire that asked how confident they were that patients understood how to correctly use the device, how they would rate each patient's experience using the device (ie, very difficult to very easy) and whether patients were able to correctly use the device by the end of the training session.

Adverse events were monitored throughout the trial and 4 weeks after study completion. Standard laboratory testing, conducted at screening and week 12, included blood chemistries, hematology and urinalysis. Special tests were also conducted at that time for ferritin, C-reactive protein, angiotensin-converting enzyme, erythrocyte sedimentation rate and hormonal and multiple additional autoimmune marker levels.

2.5 Study endpoints and statistical analysis

The primary endpoint was the proportion of patients who rated the single-use autoinjector as easy to use or very easy to use for self-injection on the user trial questionnaire at the end of 12 weeks based on their response to the question: "Overall, how do you rate your experience with using the injection device?" (question 14 of the user trial questionnaire). All of the other questions on the user trial questionnaire were prespecified as secondary endpoints. Additional secondary endpoints included trainer assessments and changes in SF-36v2 component scores. Safety endpoints included the incidence of adverse events (AEs). Primary and secondary analyses were performed on the intent-to-treat (ITT) population, defined as all patients with at least one dose of study medication. The safety analyses included all patients in the ITT population with follow-up safety data. Descriptive statistics were used to summarize all primary, secondary and safety endpoints. Statistical tests were performed at the 0.05 level of significance; all confidence intervals (CIs) were two-sided 95% CIs. No adjustments were made for multiple comparisons. All analyses were performed using Version 9.1 or higher of SAS® software. All summary tables and listings were prepared using SAS software.

The primary endpoint was evaluated by calculating a two-sided 95% CI for the proportion, using the normal approximation to the binomial distribution. Worst case imputation, where missing values were assigned the most negative response option available to the patient, was used in the case of missing data at week 12.

Secondary endpoints assessed by the user trial questionnaire were summarized as the proportion of patients rating each response to those 32 questions. Thirteen prespecified endpoints evaluated patients' satisfaction with the device, functional reliability, convenience and various device attributes, which were expressed as the proportion of patients responding positively and were analyzed using worst case imputation for missing data values at week 12 and a two-sided 95% CI for the proportion, using the normal approximation to the binomial distribution. As a sensitivity analysis, all user trial questionnaire endpoints were also presented using complete case methodology, which included only nonmissing responses at week 12 in the analysis. The quality-of-life (QoL) assessment (SF-36v2 Health Survey) was analyzed in terms of the change in score from screening to week 12.

Exploratory analyses were also conducted and included assessments of any statistical associations between baseline characteristics (based on the neurologic examinations, cognitive assessment and fatigue scale) and responses to 14 selected questions from the user trial questionnaire. Another exploratory analysis examined the association of ferritin and injection-site reactions (ISRs) with levels of inflammatory or autoimmune markers.

Effects of baseline characteristics on questionnaire responses were evaluated with a multiple logistic regression model that was fitted for each question expressed in a binary response (positive vs neutral/negative) at week 12 as the dependent variable and baseline characteristics as covariates. The baseline characteristics were categorized into binary variables (eg, normal versus non-normal). An analysis of covariance was also performed to test for an association of baseline variables with a composite score from 25 questions selected a priori from the user trial questionnaire. The potential association of autoimmune/inflammatory markers with ferritin and/or ISRs was evaluated using a Fisher's exact test.

Statistical analyses were carried out using SAS Version 9.1 or higher.

3. Results

3.1 Patient disposition and baseline characteristics

A total of 121 patients were screened for the study of whom 109 were included in the ITT population. Two patients withdrew prematurely: one owing to an AE (elevated liver function tests) and another owing to expressed difficulty with the device. Baseline and demographic characteristics are listed in **Table 1**. The average age was 46 years, 70% were women and 86% were white. Neurologic assessments demonstrated that 95 (87.2%) patients had non-normal score on at least 1 of the 72 items evaluated at study day 1, with 36.7, 51.4, 15.6, 14.6 and 13.8% of patients demonstrating non-normal results for cranial nerve status, gait status, coordination status, reflex status and sensory status, respectively. Results from the cognitive battery indicated that 108 (99.1%) patients had non-normal scores (defined as patients with probable normal, abnormal or probable abnormal scores) in at least one item, with 53.5, 50.0, 41.3 and 23.1% of patients demonstrating abnormal results (defined as probable abnormal or abnormal) for memory, global cognition, executive function and attention index scores, respectively. Furthermore, 14.7% had non-normal (defined as ≥ 5.8, indicative of MS-related fatigue) average FSS scores.

3.2 Primary endpoint

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 2**). The lower bound of the 95% CI was > 50%, indicating that the primary objective of the study was met and the majority of patients participating in the trial found the device easy or very easy to use.

3.3 Secondary endpoints

A total of 3948 single-use autoinjectors were used during the study. Results for prespecified secondary endpoints from the user trial questionnaire demonstrated a high degree of functional reliability and patient satisfaction with device attributes and convenience. Data at 12 weeks indicated that the single-use autoinjector was functionally reliable (**Figure 3**), with 105 (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

Table 1. Baseline patient characteristics.

N	109
Mean (SD) age, years	46.0 (9.32)
Sex, n (%)	
Women	76 (69.7)
Men	33 (30.3)
Race, n (%)	
White	94 (86.2)
Black	8 (7.3)
Other	7 (6.4)
Handedness, n (%)	
Right	96 (88.1)
Left	13 (11.9)
Mean (SD) weight, kg	83.8 (21.7)
Abnormal* neurologic examination, n (%)	
Cranial nerve status	40 (36.7)
Gait status	56 (51.4)
Coordination status	17 (15.6)
Reflexes status	14 (14.6)
Sensory status	15 (13.8)
Non-normal cognitive assessment, n (%)‡	
Overall global score	108 (99.1)
Global cognitive score	48 (50.0)
Attention index score	24 (23.1)
Executive function index score	43 (41.3)
Memory index score	54 (53.5)

*Deficit in ≥ 1 area of the neurologic examination.
‡Based on Neurotrax Mindstreams® (Fresh Meadows, NY) data; n (%) represents those patients with abnormal and probable abnormal findings. The denominator is 96 for global cognitive score, 104 for attention index and executive function index score, and 101 for memory index score.

91 (83% (95% CI, 77% – 90%)) patients, the device simplified injections, and 84 (77% (95% CI, 69% – 85%)) patients considered the device easy or very easy to hold (**Figure 4**).

Similar results were observed in regard to measures of satisfaction and convenience. The majority of patients reported that they were somewhat or extremely satisfied with the size of the device (Q19) (61% (95% CI, 51% – 70%)), the force required to remove the cap (Q20) (87% (95% CI, 81% – 93%)), the pressure required to activate the button for injection (Q21) (78% (95% CI, 70% – 86%)) and the time for injection (Q22) (83% (95% CI, 75% – 90%) (**Figure 4**). Most patients agreed or strongly agreed that the single-use autoinjector helped them self-administer their injections (Q6) (83% (95% CI, 75% – 90%)) and allowed for easy access to various injection sites (Q5) (78% (95% CI, 70% – 86%)) (**Figure 4**). The single-use autoinjector was considered to be somewhat convenient or extremely convenient (Q24) by 81 (74% (95% CI, 66% – 83%)) of 109 patients at 12 weeks (**Figure 4**).

Additional secondary endpoints also demonstrated favorable outcomes. Of 108 patients without missing responses at week 12, 107 (99%) indicated that the needle shield often or always covered the needle after injection, and 79 (73%) patients indicated that they would continue using the single-use autoinjector if it became available (**Table 2**). Overall convenience, ability to save time and needle shielding were the highest rated aspects of the single-use autoinjector (**Figure 5**). Questions 31 and 32 of the user trial questionnaire evaluated the ability of patients to carry out certain physical tasks, with results demonstrating that the majority of patients had little to no difficulty with activities of daily living, including dressing and lifting a full cup to the mouth (**Table 2**).

Another secondary outcome tested for any changes in the patients' QoL over the 12 weeks that they used the device. Of the eight domains evaluated by the SF-36v2 Health Survey, changes in only one domain, the "role-physical" scale (mean change from screening to week 12), were statistically significant (mean ± SD change, 1.41 ± 7.1; p = 0.0415), noting improvement in this QoL scale.

Beyond patient feedback, an additional secondary outcome of the study was to evaluate trainers' confidence that study subjects could use the device appropriately. Positive outcomes were reported by the study's trainers, who indicated at week 12 that they were moderately confident to very confident that 99.1% of the patients understood how to use the device and that 87.2% of the patients had an easy or very easy time using the device.

3.4 Exploratory analyses

Fourteen questions from the user trial questionnaire were selected a priori for multiple logistic regression analysis. Results indicated that neurologic deficits at baseline, as well as cognition and fatigue, generally had no influence on patient ratings of satisfaction, functional reliability or convenience. Only two questions had one baseline variable that was statistically significant. Patients with non-normal baseline global cognition status were less likely to rate the device as unreliable than were those with normal status (odds ratio = 0.267; p = 0.021), whereas dissatisfaction with device size was more likely among patients with non-normal gait versus those with normal gait (odds ratio = 4.2; p = 0.009). An analysis of covariance was performed to test for an association of baseline variables with a composite score from 25 questions selected a priori from the user trial questionnaire. The analysis demonstrated that patient ratings of functional reliability, satisfaction and convenience were, on average, positive irrespective of whether their baseline status was normal. With individual scores having a possible range of -50 to 50, with 0 indicating a neutral response, scores from patients with non-normal baseline status ranged from 25.5 to 49.2 and scores from patients with normal baseline status ranged from 23.0 to 46.7.

Additional exploratory analyses examined relationships of ferritin level and ISRs with autoimmune or inflammatory biomarkers. Elevated ferritin levels were observed in 14 patients at week 12; however, a Fisher's exact test demonstrated no statistically significant associations of elevated ferritin with clinical markers of autoimmunity or inflammation. There was no statistically significant correlation between ISRs and autoimmune/inflammatory markers, with the exception of

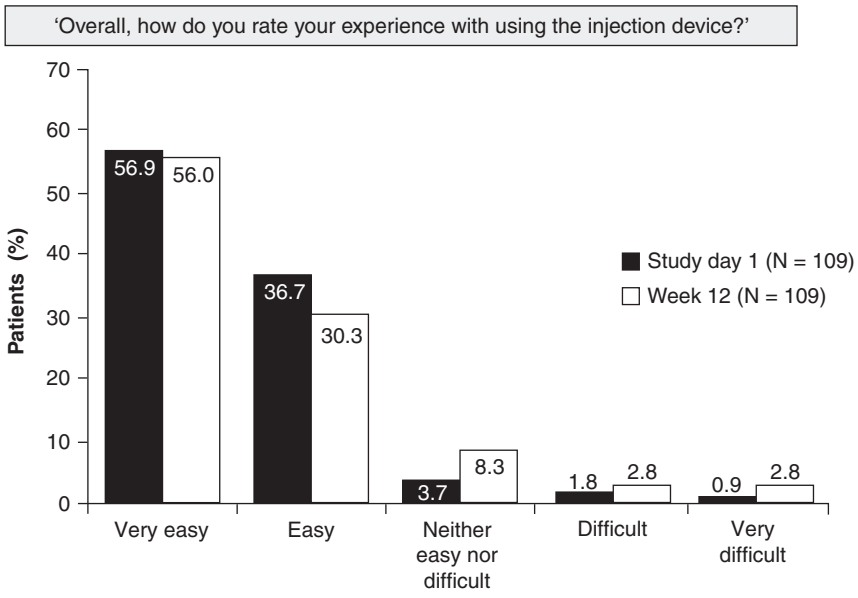

Figure 2. Primary endpoint: patient perception of the ease of the use of the single-use autoinjector at study day 1 and week 12 from the User Trial Questionnaire.

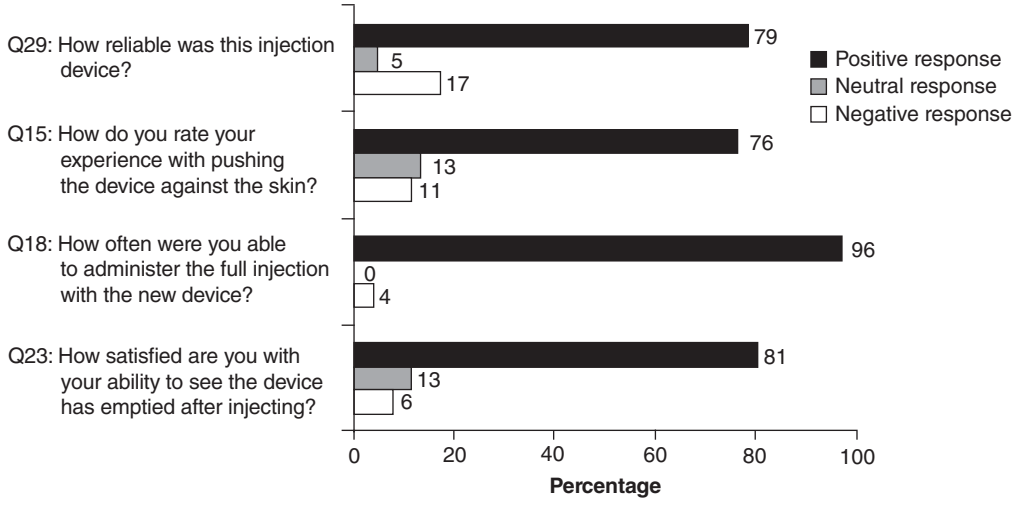

Figure 3. Patient response in functional reliability at 12 weeks from the User Trial Questionnaire.

C-reactive protein, which was elevated more frequently in patients with ISRs compared with patients without ISRs (19% (9/47 patients) versus 2% (1/61 patients); p = 0.002). There was a slight decrease in the mean (± SD) C-reactive protein value from screening (2.89 (± 4.53) mg/dL) to week 12 (2.34 (± 3.42) mg/dL). However, this change (-0.57 (± 3.22) mg/dL) was not statistically significant and was not considered to be of clinical significance, since both values were within the normal range.

3.5 Safety endpoints

At 12 weeks, 76% (83/109) of patients had at least one treatment-emergent AE (TEAE; **Table 3**). In the majority (93%) of patients who experienced TEAEs, the observed or reported events were considered mild or moderate. Five serious AEs were reported in four patients and included one occurrence each of angina pectoris, acute pancreatitis, chest pain, convulsion and hypertension. All serious AEs resolved and were considered to be unrelated or unlikely to be related to

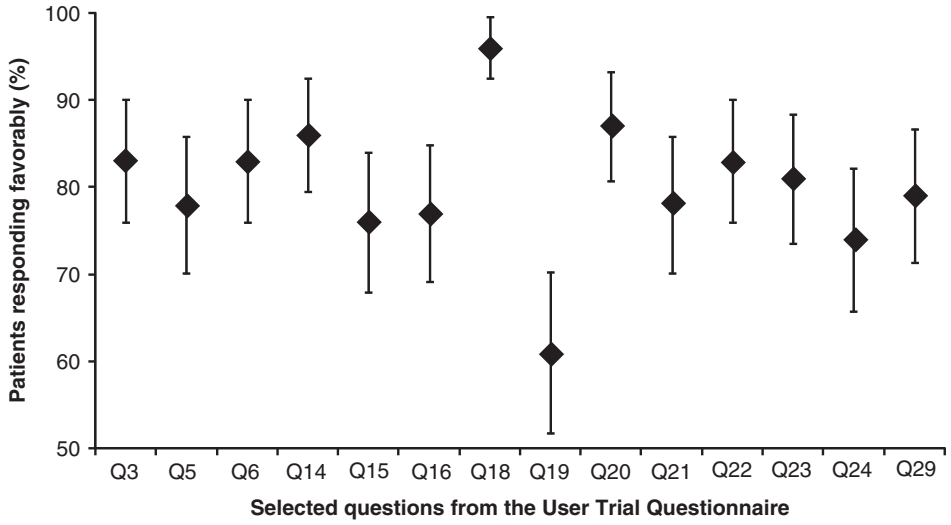

Figure 4. Proportions of patients* indicating a favorable response to selected‡ questions from the User Trial Questionnaire.
Q3: The device makes the injection simple
Q5: This device allows for easy access to various skin injection sites
Q6: This device helps me self-administer my injections
Q14: Overall, how do you rate your experience with using the injection device?
Q15: Overall, how do you rate your experience with pushing the device against the skin?
Q16: Overall, how do you rate your experience with holding the device during the injection?
Q18: How often were you able to administer the full injection with the new device?
Q19: How satisfied are you with the size of the device?
Q20: How satisfied are you with the force required to remove the cap of the device?
Q21: How satisfied are you with the pressure required to activate the button for injection?
Q22: How satisfied are you with the time it took for the needle to go into the skin and inject the medication?
Q23: How satisfied are you with your ability to see that the device has emptied after injecting?
Q24: How would you rate the convenience of this device?
Q29: How reliable was this injection device?
*Percentages calculated using worst case imputation. Error bars indicate 95% CI calculated using the normal approximation to the binomial distribution.
‡All questions not depicted here are included in **Table 2** and **Figure 5**.

treatment; no patient died during the study. The most common AEs were ISRs and flu-like symptoms, and the majority of these events were mild in severity. AEs were coded under version 13 of the Medical Dictionary for Regulatory Activities, in which all cases of injection-site bruising are coded as "injection-site hematoma." Injection-site bruising accounted for all cases of injection-site hematoma reported in **Table 3**.

4. Discussion

The MOSAIC study evaluated the potential of a single-use autoinjector to improve the self-injection experience among patients with relapsing MS undergoing treatment with IFNβ-1a 44 μg sc. Study endpoints primarily served to evaluate patient responses to a user trial questionnaire, which was developed by physicians in conjunction with a team of device and questionnaire experts and tested in a representative "real-world" sample of MS patients before the study. Similar questionnaires have been used by previous studies to evaluate device usability [5,13].

Overall, the single-use autoinjector was well received by the MS patients evaluated in the study. The primary objective was met, with 86% (95% CI, 80% – 93%) reporting that the device was easy or very easy to use after 12 weeks. The majority of patients also rated the single-use autoinjector favorably on all other items from the user trial questionnaire, and evaluation of secondary endpoints demonstrated high ratings of functional reliability, patient satisfaction with the device, convenience, simplicity and specific attributes of the device. At week 12, study personnel also reported a high level of confidence that patients understood how to use the device and had an easy time using the device. Changes in SF-36v2 component scores were included as a secondary endpoint. Only the role-physical scale in the QoL survey instrument demonstrated a statistically significant improvement from screening to week 12. The small magnitude of change, short duration of the study and absence of change in the other seven subscales of the SF-36v2 make this a finding of uncertain clinical significance. No decrease in patient-perceived QoL was noted in any of the SF-36v2 subscales.

Table 2. Additional* secondary endpoints: responses to questions from the User Trial Questionnaire.

Question	Positive rating‡	Response options
1. This device allows me to know for sure when the injection had been completed	88%	**2 = Strongly agree**
2. I find that the features of this device help me minimize safety hazards (pre- and postinjection)	84%	**1 = Agree**
4. I would feel comfortable using this device away from home	88%	0 = Neither agree nor disagree
7. This injection device enhances my ability to take my medication when I am supposed to	62%	-1 = Disagree
8. The ready-to-use format is a key attraction/benefit of this device	87%	
9. The automatic needle retraction is a key feature/benefit of this device	74%	-2 = Strongly disagree
10. It was convenient to store this injection device	65%	
11. With this device, I am confident that I performed the injection correctly	87%	
12. I am confident that I am injecting a complete dose of medication with this device	86%	
13. My trainer provided easily understandable, unbiased and practical information about the proper injection method using the injection device	98%	
17. How often did the device needle shield completely cover the needle after the injection was completed?	99%	2 = Always **1 = Often** -1 = Sometimes -2 = Never
26. Would you continue using the injection device after this study if it were available?	73%	Yes/no
27. Would you use the injection device only under special circumstances (for example, only when traveling)?	32%	
28. How likely would you be to recommend this injection device to others needing Rebif® therapy?	69%	**2 = Very likely** **1 = Likely** 0 = Neutral opinion -1 = unlikely -2 = Very unlikely
30. Prior to entering this study, which kind of injection method were you using?	0, 17% 1, 74% 2, 9%	0 = Manual injection 1 = Rebiject 2 = Both
31. How much difficulty do you have dressing yourself, including tying shoelaces and doing buttons?	94%	**0 = No difficulty at all** **1 = Little difficulty**
32. How much difficulty do you have lifting a full cup or glass to your mouth?	99%	2 = Moderate difficulty 3 = A great deal of difficulty

*Primary endpoint (Question 14) and other questions not displayed here are contained in **Figures 4** and **5**.

‡Determined as the percentage of patients responding with one of the two best ratings for each rating scale or the percentage of patients responding "Yes" for questions with "Yes/no" responses (responses shown in bold).

No new safety concerns were demonstrated in the MOSAIC study, and AEs were consistent with the known safety profile for IFNβ-1a 44 μg sc tiw. The most common AEs were ISRs and flu-like symptoms. Exploratory analyses of the potential associations of autoimmune and/or inflammatory markers with ferritin levels and ISRs demonstrated no statistically significant correlations, except between ISR incidence and levels of C-reactive protein. Failure to observe correlations of ferritin and ISRs with other clinical laboratory parameters may be due to the small number of patients with abnormal clinical laboratory values.

Patients in this study underwent extensive neurologic and cognitive screening before entering the study. Cognitive abnormalities were common; 54 (53.5%) patients had a memory index score, 48 (50.0%) had a global cognition score, 43 (41.3%) had an executive function index score, and 24 (23.1%) had an attention index score that was considered abnormal (≤ 85) or probable abnormal (> 85 to ≤ 96.25). In addition, the majority of patients (87.2%) had some degree of neurologic impairment. Taken with the demographic profile reflected in **Table 1**, these findings establish the study population as likely to be representative of the general MS population that would be expected to self-inject. Furthermore, results from an exploratory analysis demonstrated that there were no statistically significant associations between baseline neurologic deficits (ie, cognition, visual function or dominant upper extremity function) and patient ratings of ease of use, underscoring the usability of the autoinjector in a representative MS population with a wide range of neurologic and cognitive deficits. Despite the lack of a control group in this study limiting the overall interpretation of results, the favorable user perceptions of the single-use autoinjector are encouraging in view of continuing efforts to enhance patient adherence to injectable medication. Although no studies have yet

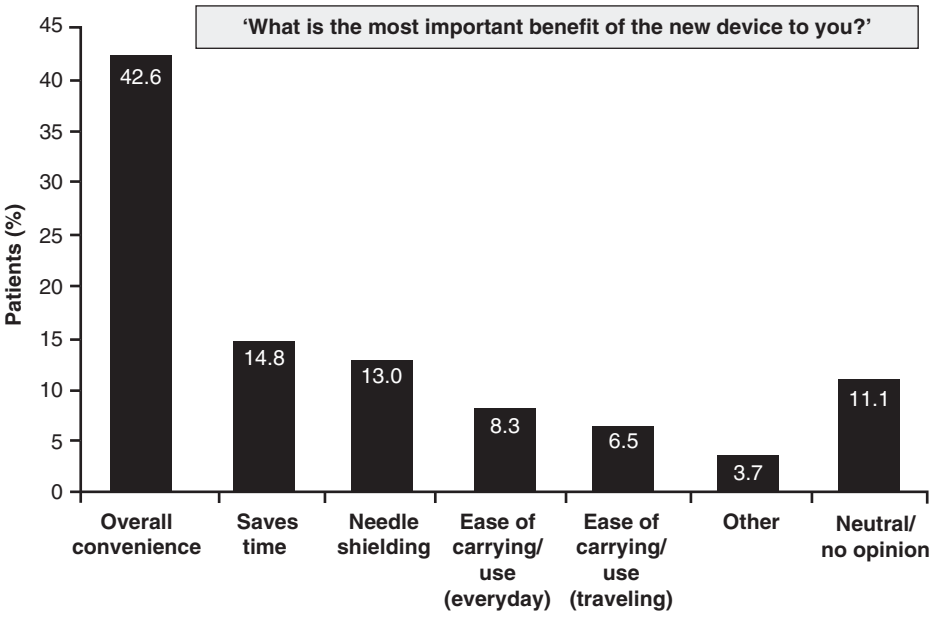

Figure 5. Patient evaluation of most important benefits of the device at week 12 from the User Trial Questionnaire. Response at week 12 from question 25 of the user trial questionnaire (n = 108, non-missing responses).

Table 3. Summary of TEAEs*.

	Patients, n (%)*
N	109
Any AE	83 (76)
Injection-site erythema	39 (36)
Injection-site pain	27 (25)
Influenza-like illness	26 (24)
Injection-site hematoma‡	13 (12)
Injection-site swelling	8 (7)
Headache	7 (6)
Upper respiratory tract infection	6 (5)

*Includes only those events reported in > 5% of patients.
‡Injection-site bruising accounted for all cases of injection-site hematoma (see text for explanation).
AE: Adverse event; TEAE: Treatment-emergent adverse event.

demonstrated a direct improvement of adherence to MS therapy with autoinjector devices, accumulating evidence indicates that such devices have the potential to attenuate factors known to affect discontinuation [13,14]. The currently available autoinjectors for sc administration of IFNβ-1a are designed to provide a range of options that address the diversity of patients' individual needs. Introduction of this single-use autoinjector provides a further option with additional features: its single-use nature makes its day-to-day use straightforward and the device lacks complexity, the transparent design of the plastic syringe housing enables 360° inspection of the contents of the autoinjector and the device has a needle-shielding mechanism that automatically covers the needle before and after injection to reduce the risk of inadvertent needle sticks. Furthermore, this single-use autoinjector has an internal locking mechanism that prevents activation of the device unless the injector is firmly applied onto the injection site and the injector button is simultaneously pressed. The favorable patient perception of this single-use device has particular relevance to the landscape of therapeutic options for MS in the United States, where, in contrast to several European countries, no single-use autoinjectors are currently offered to patients.

Potential limitations of the current study include its short duration (12 weeks) and the lack of a control group. Whether the perceived benefits of the device as well as the level of patient-perceived QoL would persist with continued use or whether the benefits would be limited by disease progression is not clear. Whether patients naive to injectable disease-modifying drugs, or those in the process of titrating the drug, would share the favorable perception of the device as compared with patients who are experienced in self-injecting IFNβ-1a sc is also uncertain. The small size of the study population was another limitation and may have contributed to the small magnitude of change in the SF-36v2 scores and the lack of clear relationship of elevated ferritin levels with immune or inflammatory markers.

In conclusion, results from the MOSAIC study demonstrated that the single-use autoinjector was associated with a favorable degree of acceptability among patients with relapsing MS receiving IFNβ-1a sc tiw therapy and that most patients said they would continue to use the

device if it became available, suggesting that the device may be associated with improvements in the overall injection experience.

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