# Supplemental Online Content

This supplemental material has been provided by the authors to give readers additional information about their work.

**eAppendix.** Patient-Reported Outcomes

**Methods**

Fatigue was measured by the Pediatric Quality of Life Inventory (PedsQL) Multidimensional Fatigue Scale scores (containing 18 questions in 3 fatigue dimensions: general fatigue, sleep/rest fatigue, and cognitive fatigue) and quality of life was measured by the PedsQL Quality of Life Scale scores (containing 23 questions in 4 dimensions: physical functioning, emotional fatigue, social fatigue, and school fatigue). In the PedsQL Multidimensional Fatigue Scale, a higher total score indicated fewer problems, and in the PedsQL Quality of Life Scale, a higher score indicated a better quality of life. Scoring for each question was based on a 5-point Likert scale from 0 (Never) to 4 (Almost always). Each individual score was then reversed (subtracted from 4) and linearly transformed as follows: 0 = 100, 1 = 75, 2 = 50, 3 = 25, 4 = 0. For each dimension, the total score was calculated as the sum of all the items divided by the number of items answered. Statistical analyses included evaluation of $P$ values at each time point based on an ANCOVA model, with dimensional fatigue score as the dependent variable and with fixed effects of treatment group, age group, and baseline dimensional fatigue score as a covariates.

**Results**

There was no trend in fatigue (fatigue was assessed using the PedsQL Multidimensional Fatigue Scale) for the comparison between the dimethyl fumarate (DMF) and interferon beta-1a (IFNβ-1a) treatment groups There were also no trends in the mean or adjusted mean scores in any of the 3 fatigue dimensions during the study in either the patients' assessments or the parent/legal guardians' assessments (**eTable 1**). The mean and adjusted mean scores were generally similar between the treatment groups and similar between patient and parent/legal guardian assessments.

Quality of life was assessed using the PedsQL Quality of Life Scale. There were no trends in the mean or adjusted mean scores in any of the 4 dimensions during the study in either the patients' assessments or the parent/legal guardians' assessments (**eTable 2**). For the patients' and parent/legal guardians' assessments, the mean and adjusted mean scores were generally similar between treatment groups with a few exceptions.

**eTable 1.** Pediatric Quality of Life Inventory Multidimensional Fatigue Scale Scores Comparisons With Scores for Participant Self-report and Parent Proxy Report

| Multidimensional Fatigue Scale, mean (SD) | Baseline | | Week 24 | | | Week 48 | | | Week 72 | | | Week 96 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | DMF | IFNβ-1a | DMF | IFNβ-1a | P | DMF | IFNβ-1a | P | DMF | IFNβ-1a | P | DMF | IFNβ-1a | P |
| **Self-assessment** | | | | | | | | | | | | | | |
| General fatigue | 71.4 (24.3) | 74.7 (20.4) | 70.2 (22.0) | 70.9 (22.2) | .63 | 71.3 (20.3) | 72.7 (20.8) | .32 | 69.2 (22.5) | 74.8 (21.1) | .59 | 69.2 (23.6) | 74.4 (19.9) | .35 |
| Sleep/rest fatigue | 67.9 (20.7) | 65.1 (22.6) | 66.3 (20.3) | 63.7 (21.5) | .27 | 67.9 (21.1) | 68.9 (20.9) | .81 | 66.5 (22.7) | 69.9 (20.8) | .74 | 67.0 (22.6) | 69.2 (20.4) | .48 |
| Cognitive fatigue | 68.4 (24.9) | 74.2 (21.3) | 71.6 (22.1) | 71.0 (24.3) | .18 | 68.4 (23.3) | 72.7 (21.4) | .72 | 68.0 (25.0) | 72.2 (20.1) | .59 | 68.1 (23.7) | 72.5 (23.2) | .74 |
| **Parent assessment** | | | | | | | | | | | | | | |
| General fatigue | 69.2 (24.1) | 72.6 (22.4) | 70.6 (21.5) | 66.9 (23.8) | .46 | 73.2 (22.5) | 68.8 (22.7) | .007[a] | 73.5 (21.3) | 73.0 (23.4) | .37 | 71.1 (22.6) | 75.3 (18.7) | .78 |
| Sleep/rest fatigue | 69.1 (24.0) | 67.9 (24.3) | 69.1 (22.5) | 68.1 (24.5) | .79 | 70.5 (23.9) | 69.7 (21.0) | .45 | 68.8 (23.9) | 72.8 (20.4) | .87 | 71.8 (20.8) | 69.8 (20.8) | .47 |
| Cognitive fatigue | 71.0 (27.3) | 76.9 (21.0) | 74.8 (23.2) | 72.8 (23.8) | .11 | 73.7 (23.4) | 76.5 (21.1) | .48 | 73.6 (22.1) | 76.1 (20.0) | .90 | 71.2 (26.9) | 75.0 (20.2) | .45 |

Abbreviations: DMF, dimethyl fumarate; IFNβ-1a, interferon beta-1a; ; PedsQL, Pediatric Quality of Life Inventory; SDS, standard deviation

[a]Statistically significant(P < .05). Higher scores equal fewer problems (less fatigue).

*P* values at each time point were based on ANCOVA model, with dimensional fatigue score as the dependent variable and with fixed effects of treatment group, age group, and baseline dimensional fatigue score as a covariates.

**eTable 2.** Pediatric Quality of Life Inventory Quality of Life Scale Score Comparisons With Participant Self-report and Parent Proxy-Report

| Multidimensional QoL Scale, mean (SD) | Baseline | | Week 24 | | | Week 48 | | | Week 72 | | | Week 96 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | DMF | IFNβ-1a | DMF | IFNβ-1a | P | DMF | IFNβ-1a | P | DMF | IFNβ-1a | P | DMF | IFNβ-1a | P |
| **Self-assessment** | | | | | | | | | | | | | | |
| About my health and activities | 77.1 (22.0) | 79.1 (18.1) | 79.1 (17.3) | 77.5 (20.7) | .19 | 77.6 (19.6) | 81.7 (17.3) | .87 | 77.7 (21.1) | 81.0 (15.7) | .73 | 79.2 (19.4) | 83.1 (16.4) | .05 |
| About my feelings | 65.6 (25.4) | 73.5 (18.9) | 70.9 (22.6) | 70.8 (20.5) | .42 | 70.4 (24.5) | 71.8 (21.5) | .26 | 69.6 (24.8) | 72.8 (20.1) | .41 | 67.5 (24.5) | 74.4 (21.3) | .005ᵃ |
| How I get along with others | 86.6 (19.4) | 87.9 (15.1) | 87.1 (16.6) | 88.0 (15.4) | .96 | 85.1 (20.2) | 90.0 (15.6) | .84 | 86.7 (17.3) | 92.0 (11.4) | .62 | 86.8 (17.4) | 93.6 (10.3) | .03ᵃ |
| About work or school | 63.9 (24.7) | 69.6 (17.8) | 68.0 (21.4) | 66.8 (22.4) | .20 | 69.0 (21.7) | 70.3 (19.6) | .30 | 66.1 (23.2) | 71.8 (18.2) | .33 | 68.5 (21.2) | 70.7 (21.5) | .58 |
| **Parent assessment** | | | | | | | | | | | | | | |
| Physical functioning | 75.6 (24.5) | 75.6 (19.9) | 78.0 (21.7) | 75.9 (20.3) | .49 | 75.1 (22.5) | 75.5 (19.8) | .15 | 74.6 (20.3) | 79.6 (19.3) | .44 | 78.3 (22.1) | 83.1 (14.9) | .47 |
| Emotional functioning | 63.8 (23.9) | 70.3 (20.3) | 67.2 (22.6) | 68.0 (19.3) | .34 | 70.5 (23.2) | 69.3 (19.6) | .03ᵃ | 69.7 (23.0) | 73.4 (17.3) | .81 | 68.1 (24.4) | 73.0 (23.6) | .79 |
| Social functioning | 83.3 (22.6) | 87.0 (17.5) | 86.0 (17.1) | 86.2 (15.5) | .91 | 82.4 (21.4) | 88.2 (17.7) | .63 | 87.4 (19.5) | 84.0 (19.8) | .10 | 86.7 (19.9) | 90.7 (15.2) | .46 |
| Work/study/school functioning | 64.6 (28.0) | 69.4 (19.0) | 68.0 (23.8) | 66.1 (19.1) | .06 | 68.2 (22.9) | 71.5 (19.9) | .09 | 68.8 (21.3) | 69.7 (19.2) | .68 | 71.3 (23.1) | 73.9 (17.6) | .55 |

Abbreviations: DMF, dimethyl fumarate; IFNβ-1a, interferon beta-1a; PedsQL, Pediatric Quality of Life Inventory; QoL, quality of life; SD, standard deviation.
ᵃStatistically significant (P < .05). Higher scores equal fewer problems (better QoL).
P value at each time point were based on ANCOVA model, with dimensional fatigue score as the dependent variable and with fixed effects of treatment group, age group, and baseline dimensional QoL score as a covariates.

**eTable 3.** Baseline and Demographic Patient Characteristics in Completers Population
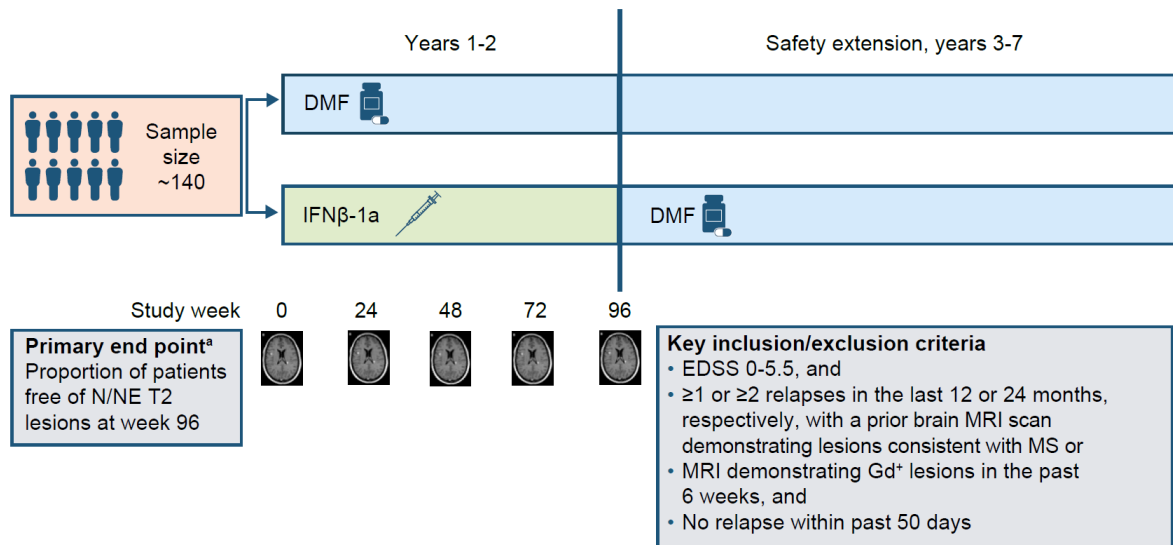
| | IFNβ-1a n = 41 | DMF n = 62 | Total N = 103 |
|---|---|---|---|
| Age category, y (%) | | | |
|   10-12 | 5 (12) | 7 (11) | 12 (12) |
|   13-14 | 5 (12) | 16 (26) | 21 (20) |
|   15-17 | 31 (76) | 39 (63) | 70 (68) |
| Age, y | | | |
|   Mean (SD) | 15.1 (1.61) | 14.8 (1.71) | 14.9 (1.67) |
|   Median (IQR) | 16.0 (15.0-16.0) | 15.0 (14.0-16.0) | 15.0 (14.0-16.0) |
|   Min, max | 11, 17 | 10, 17 | 10, 17 |
| Sex, no. (%) | | | |
|   Male | 13 (32) | 23 (37) | 36 (35) |
|   Female | 28 (68) | 39 (63) | 67 (65) |
| Race, no. (%) | | | |
|   Asian | 0 | 1 (2) | 1 (<1) |
|   Not reported due to confidentiality regulations | 14 (34) | 24 (39) | 38 (37) |
|   Other | 0 | 1 (2) | 1 (<1) |
|   Unknown/missing | 17 (41) | 29 (47) | 46 (45) |
|   White | 10 (24) | 7 (11) | 17 (17) |
| Weight, kg | | | |
|   Mean (SD) | 64.1 (12.6) | 64.8 (15.6) | 64.5 (14.4) |
|   Median (IQR) | 63.0 (56.0-71.0) | 63.8 (53.6-73.0) | 63.5 (54.0- 72.0) |
|   Min, max | 36.0, 95.4 | 36.6, 112.0 | 36.0, 112.0 |
| Height, cm | | | |
|   Mean (SD) | 166.4 (9.0) | 164.4 (8.2) | 165.2 (8.6) |
|   Median (IQR) | 165.3 (161.0-173.0) | 164.0 (160.0-170.0) | 164.8 (160.0-172.0) |
|   Min, max | 146, 185 | 143, 180 | 143, 185 |
| Time since first MS symptoms, y[a] | | | |
|   Mean (SD) | 1.2 (1.3) | 1.8 (1.9) | 1.6 (1.7) |
|   Median (IQR) | 1.0 (0.0-2.0) | 1.0 (1.0-2.0) | 1.0 (1.0-2.0) |
|   Min, max | 0, 6 | 0, 10 | 0, 10 |
| Time since diagnosis of MS, y[a] | | | |
|   Mean (SD) | 0.5 (0.6) | 1.0 (1.5) | 0.8 (1.2) |
|   Median (IQR) | 0.0 (0.0-1.0) | 1.0 (0.0-1.0) | 1.0 (0.0-1.0) |

| | | | |
|---|---|---|---|
| Min, max | 0, 2 | 0, 7 | 0, 7 |
| Number of relapses within past 12 months[a] | | | |
| Mean (SD) | 1.5 (0.6) | 1.6 (0.9) | 1.5 (0.8) |
| Median (IQR) | 1.0 (1.0-2.0) | 1.0 (1.0-2.0) | 1.0 (1.0-2.0) |
| Min, max | 1, 3 | 0, 5 | 0, 5 |
| Baseline EDSS score | | | |
| Mean (SD) | 1.1 (1.0) | 1.2 (1.1) | 1.2 (1.1) |
| Median (IQR) | 1.0 (0.0-1.5) | 1.0 (0.0-2.0) | 1.0 (0.0-2.0) |
| Min, max | 0, 4 | 0, 5 | 0, 5 |
| T1 lesion volume (mL)[a] | | | |
| Mean (SD) | 1.0 (1.9) | 1.4 (2.0) | 1.2 (2.0) |
| Median (IQR) | 0.3 (0.1-1.0) | 0.7 (0.1-1.3) | 0.4 (0.1-1.3) |
| Min, Max | 0.0, 9.9 | 0.0, 8.8 | 0.0, 9.9 |
| T2 lesion volume (mL)[a] | | | |
| Mean (SD) | 6.0 (7.3) | 8.8 (10.4) | 7.7 (9.3) |
| Median (IQR) | 2.6 (1.3-8.0) | 5.5 (2.4-10.6) | 4.8 (1.5-9.8) |
| Min, max | 0.1, 31.5 | 0.3, 47.1 | 0.1, 47.1 |
| T2 lesion count | | | |
| Mean (SD) | 35.1 (32.1) | 47.6 (38.6) | 42.6 (36.5) |
| Median (IQR) | 24.0 (16.0-44.0) | 35.5 (21.0-67.0) | 27.0 (18.0-62.0) |
| Min, Max | 2.0, 152.0 | 5.0, 172.0 | 2.0. 172.0 |
| Gadolinium+ lesion count[a] | | | |
| Mean (SD) | 2.4 (6.1) | 2.1 (3.2) | 2.2 (4.6) |
| Median (IQR) | 0.0 (0.0-2.0) | 1.0 (0.0-3.0) | 1.0 (0.0-3.0) |
| Min, Max | 0.0, 37.0 | 0.0, 16.0 | 0.0, 37.0 |

Abbreviations: DMF, dimethyl fumarate; EDSS, Expanded Disability Status Scale; IFNβ-1a, interferon beta-1a; IQR, interquartile range.

[a]n=61 for DMF group

Completers population comprised patients who received treatment for 96 weeks and had an MRI at week 96.

**eTable 4.** Summary of Treatment-Emergent Adverse Events in Intention-to-Treat Population

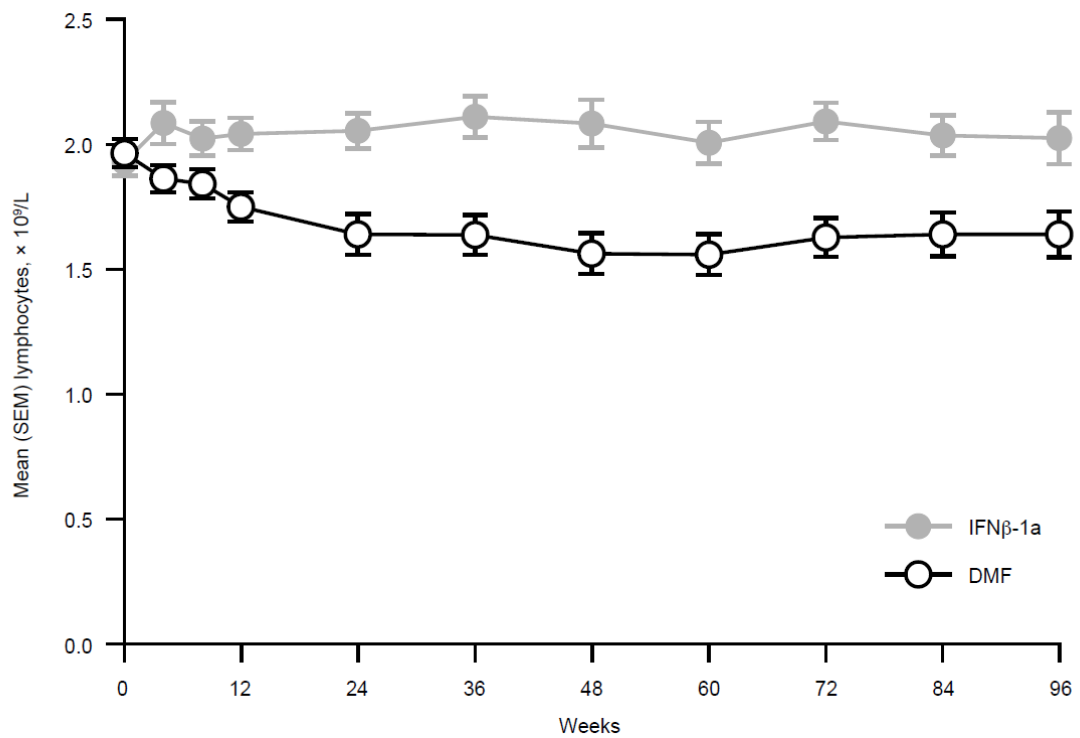| Treatment-emergent adverse events | IFNβ-1a n = 72 | DMF n = 78 | Total N = 150 |
|---|---|---|---|
| Number of patients with any adverse event, no. (%) | 69 (96) | 74 (95) | 143 (95) |
| Severity of adverse event, no. (%)[a] | | | |
|     Mild | 27 (38) | 29 (37) | 56 (37) |
|     Moderate | 32 (44) | 42 (54) | 74 (49) |
|     Severe | 10 (14) | 3 (4) | 13 (9) |
| Serious adverse event, no. (%) | 21 (29) | 18 (23) | 39 (26) |
| Adverse events leading to drug withdrawal, no. (%) | 8 (11) | 5 (6) | 13 (9) |
| Adverse events leading to study discontinuation, no. (%) | 8 (11) | 5 (6) | 13 (9) |
| Abbreviations: DMF, dimethyl fumarate; IFNβ-1a, interferon beta-1a;; ITT, intent-to-treat. [a]Each patient counted once at maximum severity. A patient can appear in >1 category. | | | |

**eFigure 1.** CONNECT Study Design



Abbreviations: DMF,dimethyl fumarate; EDSS, Expanded Disability Status Scale; Gd+, gadolinium-enhancing; IFNβ-1a, interferon beta-1a; MRI, magnetic resonance imaging; MS, multiple sclerosis; N/NE, new or newly enlarging.

[a]Completers population: patients who completed week 96 of the study and who had MRI data for week 96.

**eFigure 2.** Mean Lymphocyte Count Over 96-Week Treatment Period



Mean and SEM lymphocyte countover study duration are shown. Sample size is listed by time point.

Abbreviations: DMF,dimethyl fumarate; IFNß-1a, interferon beta-1a; SEM, standard error of the mean.