ON-LINE APPENDIX: METHODS

Patient Population

In the double-blind phase, the patients received treatment with intramuscular interferon β-1a (30 μg/week) alone or in combination with azathioprine (50 mg/day) or azathioprine plus prednisone (10 mg every other day). At the end of the double-blind phase, patients with MS entered first a 3-year extension[1,2] and then a subsequent 5-year extension[3] of studies during which they continued monotherapy with intramuscular interferon β-1a, added other therapies to intramuscular interferon β-1a, or switched to new therapies. At the 10-year follow-up, 74 (42%) were still on intramuscular interferon-β 1a therapy, while 79 (44.9%) switched to other disease-modifying treatments and 23 (13.1%) discontinued disease-modifying treatment.[3] Because there were no significant treatment differences regarding clinical or MR imaging outcomes during the double-blind study,[4] no subsequent subanalyses according to the original treatment status were performed in the extension phases of the study.[1-3]

MR Imaging Acquisition and Analysis

T2-LV and its absolute change were calculated using a semiautomated edge detection contouring/thresholding technique.[5] The overall number of new and enlarging T2 lesions among all time points was calculated, as previously described.[6] The normalized brain volume, normalized cortical volume, and normalized ventricle volume were measured using SIENAX,[7] while the percentage brain volume change was analyzed using SIENA (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/SIENA)[7]; the percentage cortical volume change, using SX-MTP3[8]; and percentage ventricle volume change, using VIENA (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/SIENA/UserGuide).[9]

REFERENCES

1. Horakova D, Cox JL, Havrdova E, et al. **Evolution of different MR imaging measures in patients with active relapsing-remitting multiple sclerosis over 2 and 5 years: a case-control study.** *J Neurol Neurosurg Psychiatry* 2008;79:407–14 CrossRef Medline
2. Zivadinov R, Bergsland N, Dolezal O, et al. **Evolution of cortical and thalamus atrophy and disability progression in early relapsing-remitting MS during five years.** *AJNR Am J Neuroradiol* 2013;34:1931–39 CrossRef Medline
3. Zivadinov R, Uher T, Hagemeier J, et al. **A serial 10-year follow-up study of brain atrophy and disability progression in RRMS patients.** *Mult Scler* 2016;22:1709–18 CrossRef Medline
4. Havrdova E, Zivadinov R, Krasensky J, et al. **Randomized study of interferon beta-1a, low-dose azathioprine, and low-dose corticosteroids in multiple sclerosis.** *Mult Scler* 2009;15:965–76 CrossRef Medline
5. Zivadinov R, Heininen-Brown M, Schirda CV, et al. **Abnormal subcortical deep-gray matter susceptibility-weighted imaging filtered phase measurements in patients with multiple sclerosis: a case-control study.** *Neuroimage* 2012;59:331–39 CrossRef Medline
6. Zivadinov R, Havrdova E, Bergsland N, et al. **Thalamic atrophy is associated with development of clinically definite multiple sclerosis.** *Radiology* 2013;268:831–41 CrossRef Medline
7. Smith SM, Zhang Y, Jenkinson M, et al. **Accurate, robust, and automated longitudinal and cross-sectional brain change analysis.** *Neuroimage* 2002;17:479–89 CrossRef Medline
8. Dwyer MG, Bergsland N, Zivadinov R. **Improved longitudinal gray and white matter atrophy assessment via application of a 4-dimensional hidden Markov random field model.** *Neuroimage* 2014;90:207–17 CrossRef Medline
9. Vrenken H, Vos EK, van der Flier WM, et al. **Validation of the automated method VIENA: an accurate, precise, and robust measure of ventricular enlargement.** *Hum Brain Mapp* 2014;35:1101–10 CrossRef Medline

On-line Table 1: MRI baseline and follow-up characteristics in patients with MS, according to the confirmed disability progression at the 10-year follow-up[a]

	Total Study Cohort (Mean) (SD)	Stable Group (Mean) (SD)	CDP Group (Mean) (SD)	Cohen d	*P* Value[b]
T2-LV baseline ($n = 176$)	7.80 (10.50)	6.10 (9.80)	9.50 (10.90)	0.33	.076
T2-LV follow-up ($n = 176$)	11.7 (12.8)	9.1 (12)	13.7 (13.2)	0.35	.062
T2-LV absolute change ($n = 153$)	3.83 (6.72)	2.89 (5.32)	4.59 (7.58)	0.26	.190
New/enlarging T2 lesions ($n = 153$)	19.50 (23.10)	18.67 (24.76)	20.03 (21.74)	0.06	.753
Atrophied T2-LV ($n = 153$)	1.11 (1.60)	0.68 (0.85)	1.54 (1.90)	0.58	<.001[c]
NBV baseline ($n = 176$)	1506.23 (80.91)	1518.40 (75.80)	1497.51 (84.30)	0.26	.523
PBVC ($n = 153$)	−6.52 (3.73)	−5.23 (3.00)	−7.52 (3.84)	0.55	<.001[c]
NCV baseline ($n = 176$)	631.1 (43.1)	637.4 (39.2)	626.9 (46)	0.25	.879
PCVC ($n = 152$)	−7.0 (3.2)	−6.2 (2.6)	−7.7 (3.5)	0.49	.001[c]
NVV baseline ($n = 176$)	41.2 (13.6)	40.1 (11.4)	42.2 (14.9)	0.16	.573
PVVC ($n = 152$)	42 (35.8)	32.4 (28.1)	49.7 (39.5)	0.50	.001[c]

Note:—NCV indicates normalized cortical volume; NVV, normalized ventricles volume; NBV, normalized brain volume.

[a] The volumes are presented in milliliters.

[b] The baseline *P* values were derived using the Student *t* test, while the follow-up changes in *P* values were calculated using analysis of covariance corrected for age, sex, and treatment change during the follow-up. The Benjamini-Hochberg correction was used to minimize the false discovery rate, and *P* values < .05 were considered significant.

[c] Significant *P* values <.05.

On-line Table 2: Time course of cumulative new/enlarging T2 lesions on serial MRI in patients with MS, according to the confirmed disability progression status at the 10-year follow-up

Months from Baseline	No. in Stable Group	New/Enlarging T2 Lesions Stable Group (Mean) (SD)	No. of Patients with CDP	New/Enlarging T2 Lesions CDP Group (Mean) (SD)	% Difference	Cohen d	*P* Value[a]
6 mo	74	1.70 (2.90)	94	2.50 (3.40)	47.1	0.25	.240
12 mo	76	3.43 (6.63)	95	4.76 (5.39)	41.2	0.23	.482
24 mo	68	5.50 (8.63)	85	7.90 (8.37)	43.6	0.28	.293
36 mo	67	7.75 (11.30)	89	11.85 (16.75)	56.6	0.30	.185
48 mo	68	9.91 (15.28)	87	13.19 (14.96)	33.3	0.22	.442
60 mo	67	12.64 (19.75)	91	15.58 (18.49)	23.8	0.16	.670
72 mo	66	14.49 (22.17)	87	16.97 (19.29)	17.2	0.12	.893
84 mo	68	15.55 (23.00)	85	17.96 (19.93)	16.1	0.12	.909
96 mo	67	16.85 (23.45)	87	18.70 (20.75)	11.3	0.09	.986
108 mo	68	17.75 (23.90)	84	19.32 (21.40)	9.7	0.07	.993
120 mo	68	18.67 (24.76)	85	20.03 (21.74)	7.0	0.06	.885

[a] *P* values, percentage difference, and Cohen d effect size represent the CDP-vs-stable group comparisons. The follow-up changes in *P* values were calculated using analysis of covariance corrected for age, sex, and treatment change at each time point. The Benjamini-Hochberg correction was used to minimize the false discovery rate, and *P* values < .05 were considered significant.

On-line Table 3: Time course of absolute T2 lesion volume changes on serial MRI in patients with MS, according to the confirmed disability progression status at the 10-year follow-up[a]

Months from Baseline	No. in Stable Group	T2-LV Absolute Change Stable Group (Mean) (SD)	No. of Patients with CDP	T2-LV Absolute Change CDP Group (Mean) (SD)	% Difference	Cohen d	*P* Value[b]
6 mo	74	0.46 (1.50)	94	0.83 (2.40)	80.4	0.18	.340
12 mo	76	0.74 (1.70)	95	1.30 (2.53)	75.7	0.26	.198
24 mo	68	1.10 (2.14)	85	1.78 (3.40)	61.8	0.24	.243
36 mo	67	1.45 (2.30)	89	2.31 (4.72)	59.3	0.23	.252
48 mo	68	1.53 (2.72)	87	2.56 (5.94)	67.3	0.22	.278
60 mo	67	1.97 (3.32)	91	2.97 (6.33)	50.8	0.20	.332
72 mo	66	2.70 (5.40)	87	3.64 (7.14)	34.8	0.15	.435
84 mo	68	2.89 (5.18)	85	4.00 (7.26)	38.4	0.18	.374
96 mo	67	2.87 (5.22)	87	4.17 (7.46)	45.3	0.20	.316
108 mo	68	2.76 (5.36)	84	4.00 (7.37)	70.5	0.19	.340
120 mo	68	2.89 (5.32)	85	4.59 (7.58)	58.8	0.26	.190

[a] The volumes are presented in milliliters.

[b] *P* values, percentage difference, and Cohen d effect size represent the CDP-vs-stable group comparisons. The follow-up changes in *P* values were calculated using analysis of covariance corrected for age, sex, and treatment change at each time point. The Benjamini-Hochberg correction was used to minimize the false discovery rate, and *P* values < .05 were considered significant.

On-line Table 4: Time course of cortical brain atrophy on serial MRI in patients with MS, according to the confirmed disability progression status at the 10-year follow-up

Months from Baseline	No. in Stable Group	PCVC Stable Group (Mean) (SD)	No. of Patients with CDP	PCVC CDP Group (Mean) (SD)	% Difference	Cohen d	*P* Value[a]
6 mo	74	−0.93 (2.16)	94	−1.13 (2.34)	21.5	0.09	.572
12 mo	76	−1.40 (2.10)	95	−1.90 (2.26)	35.7	0.23	.164
24 mo	68	−2.19 (2.56)	85	−2.83 (2.01)	29.2	0.28	.083
36 mo	67	−3 (2.50)	89	−3.34 (2.84)	11.3	0.13	.426
48 mo	68	−3.33 (2.27)	87	−4.04 (3.08)	21.3	0.26	.116
60 mo	67	−3.86 (2.67)	91	−5.08 (2.90)	31.6	0.44	.008[b]
72 mo	66	−4.09 (2.44)	87	−5.30 (3.08)	29.6	0.44	.009[b]
84 mo	68	−4.61 (2.76)	85	−5.89 (3.15)	27.8	0.43	.009[b]
96 mo	67	−5.20 (2.75)	87	−6.59 (3.15)	26.7	0.47	.005[b]
108 mo	68	−5.01 (2.64)	84	−6.72 (3.30)	34.1	0.57	.001[b]
120 mo	68	−6.22 (2.60)	84	−7.71 (3.50)	24	0.49	.001[b]

[a] *P* values, percentage difference, and Cohen effect size represent the CDP-vs-stable group comparisons. The follow-up changes in *P* values were calculated using analysis of covariance corrected for age, sex, and treatment change at each time point. The Benjamini-Hochberg correction was used to minimize the false discovery rate, and *P* values < .05 were considered significant.
[b] Significant *P* values < .05.

On-line Table 5: Time course of central brain atrophy on serial MRI in patients with MS, according to the confirmed disability progression status at the 10-year follow-up

Months from Baseline	No. in Stable Group	PVVC Stable Group (Mean) (SD)	No. of Patients with CDP	PVVC CDP Group (Mean) (SD)	% Difference	Cohen d	*P* Value[a]
6 mo	76	4.57 (6.44)	95	5.90 (6.11)	29.1	0.21	.170
12 mo	76	6.44 (8.53)	95	9.44 (10.90)	46.7	0.31	.051
24 mo	68	9.53 (9.44)	85	14.37 (15.54)	50.8	0.38	.025[b]
36 mo	67	13.38 (13.34)	89	22.55 (23.50)	68.5	0.48	.005[b]
48 mo	68	17.12 (15.56)	87	26.68 (25.09)	55.8	0.46	.007[b]
60 mo	67	18.98 (18.78)	91	33.50 (30.31)	76.5	0.57	.001[b]
72 mo	66	21.92 (20.72)	87	35.11 (31.06)	60.2	0.50	.001[b]
84 mo	68	24.82 (23.46)	85	43.52 (35.99)	75.3	0.62	<.001[b]
96 mo	67	28.96 (25.80)	87	44.30 (33.14)	52.3	0.52	.001[b]
108 mo	68	28.95 (26.77)	84	48.31 (36.23)	66.9	0.61	<.001[b]
120 mo	68	32.37 (28.11)	84	49.65 (39.51)	53.4	0.50	.001[b]

[a] *P* values, percentage difference, and Cohen effect size represent the CDP-vs-stable group comparisons. The follow-up changes in *P* values were calculated using analysis of covariance corrected for age, sex, and treatment change at each time point. The Benjamini-Hochberg correction was used to minimize the false discovery rate, and *P* values < .05 were considered significant.
[b] Significant *P* values < .05.

On-line Table 6: Time course of atrophied T2 lesion volume between consecutive MRI time points in patients with MS, according to the confirmed disability progression status at the 10-year follow-up[a]

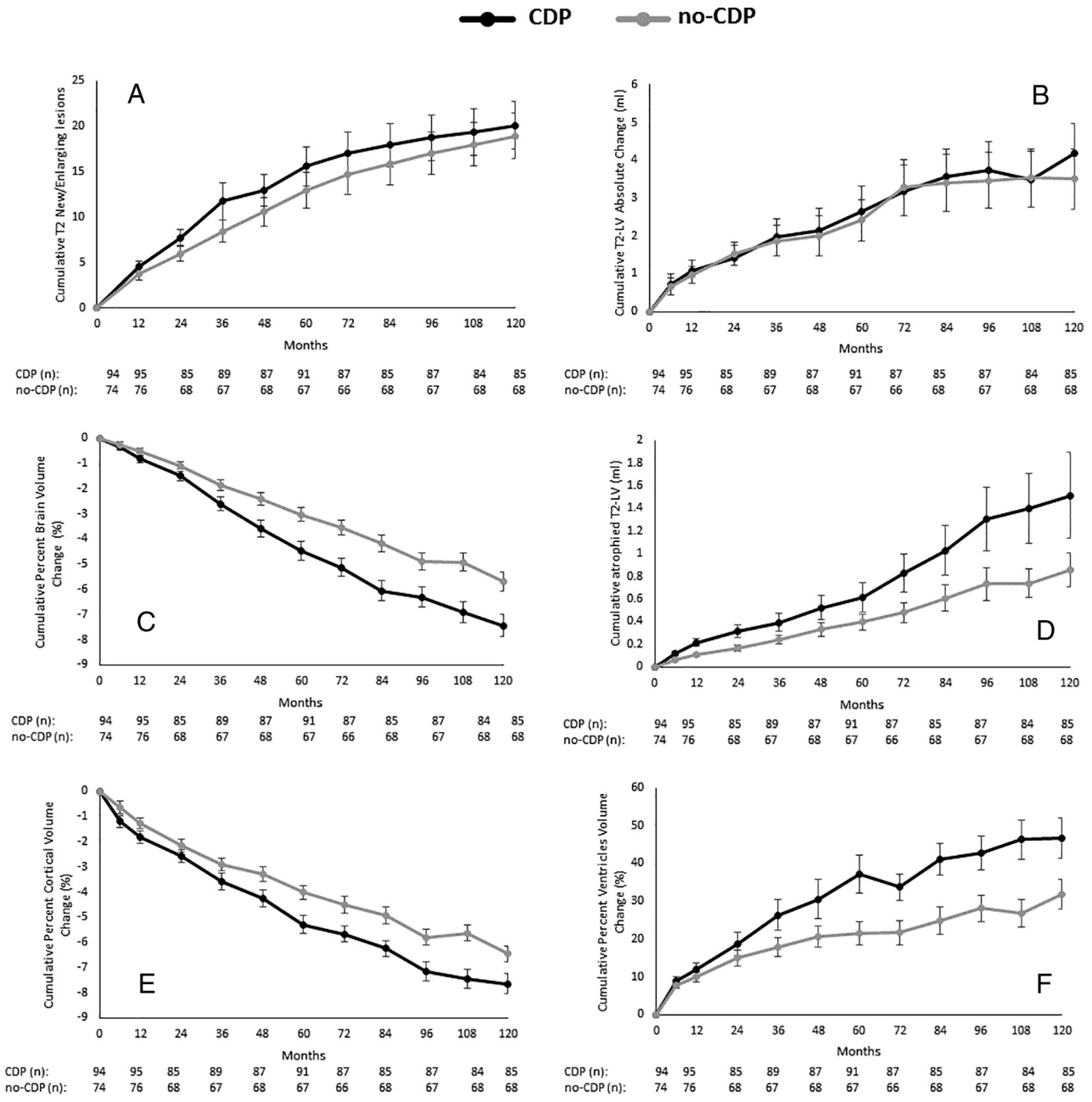
Time Points	No. in Stable Group	Atrophied T2-LV Stable Group Mean (SD)	No. of Patients with CDP	Atrophied T2-LV CDP Group Mean (SD)	% Difference	Cohen d	*P* Value[b]
0–6 mo	74	0.05 (0.09)	90	0.12 (0.16)	140	0.54	.004[c]
6–12 mo	74	0.04 (0.08)	90	0.10 (0.15)	150	0.50	.012[c]
12–24 mo	68	0.05 (0.09)	80	0.16 (0.29)	220	0.51	.004[c]
24–36 mo	62	0.08 (0.20)	76	0.14 (0.21)	75	0.29	.190
36–48 mo	62	0.08 (0.15)	79	0.17 (0.32)	112.5	0.36	.075
48–60 mo	62	0.07 (0.12)	80	0.14 (0.18)	100	0.46	.014[c]
60–72 mo	60	0.09 (0.14)	85	0.19 (0.28)	111.1	0.45	.012[c]
72–84 mo	61	0.10 (0.15)	81	0.23 (0.31)	130	0.53	.004[c]
84–96 mo	61	0.11 (0.21)	80	0.21 (0.27)	90.9	0.41	.061
96–108 mo	62	0.08 (0.20)	80	0.17 (0.20)	112.5	0.45	.007[c]
108–120 mo	64	0.08 (0.10)	79	0.20 (0.30)	150	0.54	.004[c]

[a] The volumes are presented in milliliters.
[b] *P* values, percentage difference, and Cohen d effect size represent the CDP-vs-stable group comparisons. The follow-up changes in *P* values were calculated using analysis of covariance corrected for age, sex, and treatment change at each time point. The Benjamini-Hochberg correction was used to minimize the false discovery rate, and *P* values < .05 were considered significant.
[c] Significant *P* values < .05.

On-line Table 7: Time course of whole-brain atrophy between consecutive MRI time points in patients with MS, according to the confirmed disability progression status at the 10-year follow-up

Time Points	No. in Stable Group	PBVC Stable Group (Mean) (SD)	No. of Patients with CDP	PBVC CDP Group (Mean) (SD)	% Difference	Cohen d	*P* Value[a]
0–6 mo	74	−0.24 (0.80)	94	−0.34 (1.00)	47.8	0.11	.396
6–12 mo	74	−0.24 (0.77)	90	−0.46 (0.91)	91.7	0.26	.170
12–24 mo	68	−0.50 (0.86)	80	−0.81 (1.19)	62.0	0.30	.133
24–36 mo	62	−0.74 (1.63)	76	−1.31 (1.83)	77.0	0.33	.099
36–48 mo	62	−0.65 (1.01)	79	−0.95 (1.59)	46.2	0.23	.278
48–60 mo	62	−0.53 (1.31)	80	−0.84 (1.22)	58.5	0.24	.215
60–72 mo	60	−0.50 (1.05)	85	−0.87 (1.50)	54.0	0.29	.172
72–84 mo	61	−0.53 (0.95)	81	−0.90 (1.50)	69.8	0.29	.144
84–96 mo	61	−0.64 (1.09)	80	−0.56 (1.10)	−21.4	0.07	.130
96–108 mo	62	−0.24 (0.90)	80	−0.40 (1.06)	66.7	0.16	.724
108–120 mo	64	−0.45 (0.87)	79	−0.51 (1.03)	13.3	0.06	.415

[a] *P* values, percentage difference, and Cohen d effect size represent the CDP-vs-stable group comparisons. The follow-up changes in *P* values were calculated using analysis of covariance corrected for age, sex, and treatment change at each time point. The Benjamini-Hochberg correction was used to minimize the false discovery rate, and *P* values $<$ .05 were considered significant.



ON-LINE FIGURE. Accumulation of cumulative new and enlarging T2 lesions (*A*), absolute change in T2 lesion volume (*B*), percentage brain volume change (*C*), atrophied brain lesion volume (*D*), percentage cortical volume change (*E*), and percentage ventricle volume change (*F*) during 10 years between patients with MS with and without confirmed disability progression at the follow-up. *Error bars* represent standard error of the mean.