Online Supplement

PARADIG*MS* Image Processing Software

Baseline brain volume

The brain volume at baseline was calculated using a modified version of the SienaX 5.0.4 software, which corrects the segmentation of lesional tissues to white matter. The volumes were reported in native space (i.e., not normalised using skull registration because of the artifacts this can produce in children).

Percent brain volume change

Percent brain volume change (PBVC) was measured using the Paired Jacobian Integration method *(Nakamura et al. 2017 and Guizard et al. 2015).*

The Paired Jacobian integration method consisted of the following steps: (1) skull-based intra-subject registration using pairreg (*Smith et al. 2002*), (2) transformation and resampling of both images into an isotropic halfway space using third-order spline interpolation, (3) symmetric nonlinear registration of the two affine-halfway-transformed images using Symmetric Normalization (*Avants et al. 2008*), (4) calculation of local Jacobian determinants of nonlinear displacement fields, (5) integration of nonlinear Jacobian determinants within the baseline masks obtained from FAST (*Zhang et al. 2001*), and (6) combination of the linear and nonlinear determinants from steps 1 and 5 that respectively captures the skull volume change and the brain volume change relative to the skull into a final volume percent change. This last step accounts for the different growth rates of the skull and the brain observed in adolescents by adding back any volume change due to the skull registration, effectively reporting the changes in native space.

The Jacobian determinants were calculated from numerical integration and not analytical integration of functions used for nonlinear registration. The output is a percent change in volume. No lesion filling/inpainting was used.

Gadolinium-enhancing lesion identification

Gadolinium-enhancing lesions were identified manually by two independent experts followed by a consensus read.

T2-weighted lesion identification

Candidate T2-weighted lesions were identified using the software developed at NeuroRx. This was based on a Bayesian probability tissue classification performed using multi-modal, registered, bias-field-corrected images, together with tissue probability spatial priors derived

Arnold DL, *et al. J Neurol Neurosurg Psychiatry* 2020; 91:483–492. doi: 10.1136/jnnp-2019-322138

from MNI stereotaxic models (*Francis SJ 2004*). These results were manually reviewed and corrected by experts.

New and newly enlarging T2 lesion identification

New and newly enlarging T2-weighted lesions were identified using the software developed at NeuroRx. All automated results were manually reviewed and corrected by experts (*Elliott et al. 2013*).

New T1 hypointense lesion identification

New T1-weighted hypointense lesions were identified using the software developed at NeuroRx.

New T1 hypointense lesions were defined based on voxels having a T1-weighted intensity below a predetermined levels relative to the surrounding normal appearing white matter, constrained to within the new/enlarging T2 label mask. The intensity threshold was chosen to be comparable to the gray matter. These results were manually reviewed and corrected by experts.

References:

Avants et al. Symmetric diffeomorphic image registration with cross-correlation: evaluating automated labeling of elderly and neurodegenerative brain. Med Image Anal. 2008;12(1):26-41.

Elliott et al. Temporally consistent probabilistic detection of new multiple sclerosis lesions in brain MRI. IEEE Trans Med Imaging. 2013;32(8):1490-503.

Francis SJ. Automatic lesion identification in MRI of multiple sclerosis patients. Master Thesis, McGill University, Montreal, QC. 2004.

Guizard N, Fonov VS, Garcia-Lorenzo D, Nakamura K, Aubert-Broche B, Collins DL. Spatio-temporal regularization for longitudinal registration to subject-specific 3d template. PLoS One. 2015;10(8):e0133352.

Nakamura K, Jones S, Van Hecke W, Arnold DL, de Moor C, Wager C, et al. Comparison of brain atrophy measurement techniques in a longitudinal study of multiple sclerosis patients with frequent MRIs. Neurology. 2017;16 Supplement:376.

Smith et al. Accurate, robust, and automated longitudinal and cross-sectional brain change analysis. Neuroimage. 2002;17(1):479-89.

Zhang et al. Segmentation of brain MR images through a hidden Markov random field model and the expectation-maximization algorithm. IEEE Trans Med Imaging. 2001;20(1):45-57.

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Table S1. Scanner-specific MRI sequence parameters

	Sequence Type	TR (ms)	TE (ms)	ETL/Turbo Factor	NEX/NSA	Bandwidth
a. Scanner-specific PDW sequence parameters						
Siemens 1.5T	2D TSE	2000–2980	12–13	3	1	130 Hz/px
Siemens 3T	2D TSE	2200	10	4	1	181 Hz/px
GE 1.5T	2D TSE	2000–2900	12	3	1	15.63 kHz
GE 3T	2D TSE	2400–3000	8–10	3	1	22.73 kHz
Philips 1.5T	2D TSE	2200	15	3	1	Water-fat shift=2
Philips 3T	2D TSE	2200	10	3	1	Water-fat shift=3
Toshiba 1.5T	FSE+12_slt(4)	2400	12	4	1	-
Other models	2D TSE	2200	13–15	4	1	-
b. Scanner-specific T2W sequence parameters						
Siemens 1.5T	2D TSE	5750–6100	70–90	7	1	130 Hz/px
Siemens 3T	2D TSE	4500	83	11	1	219 Hz/px
GE 1.5T	2D TSE	5120	77–84	8	1	15.63 kHz
GE 3T	2D TSE	5300	60–80	8	1	22.73 kHz
Philips 1.5T	2D TSE	4900	80	8	1	Water-fat shift=2

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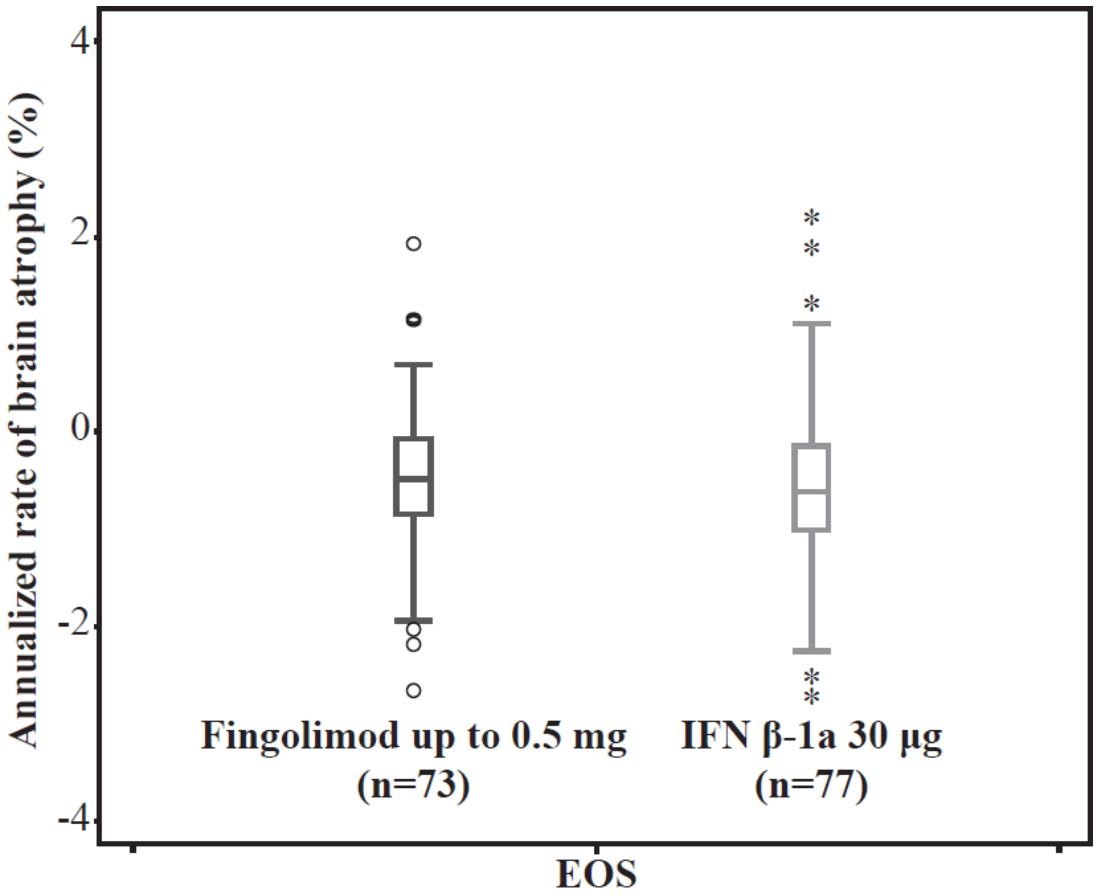
Philips 3T	2D TSE	6100	80	8	1	Water-fat shift=3
Toshiba 1.5T	FSE+10_nBW_slt (15)	5000	80	15	1	-
Other models	2D TSE	6560	84	8	1	130 Hz/px
c. Scanner-specific T1W sequence parameters						
	Sequence Type	**TR (ms)**	**TE (ms)**	**NEX/NSA**	**Flip Angle (°)**	**Bandwidth**
Siemens 1.5T	3D FLASH	30	7 or 11	1	30	70 Hz/px
Siemens 3T	3D FLASH	28	6	1	27	160 Hz/px
GE 1.5T	3D SPGR	30	7	1	30	15.6 kHz
GE 3T	3D SPGR	30	6	1	27	31.25 kHz
Philips 1.5T	3D FFE with "T1 contrast" enabled	30	7	1	30	Water-fat shift =2
Philips 3T	3D FFE with "T1 contrast" enabled	28	6	1	27	Water-fat shift=3
Toshiba 1.5T	FE3D_fc	30	7	1	30	122 Hz/px
Other models	3D FFE	30	7	1	30	70 Hz/px
d. Scanner-specific FLAIR sequence parameters						
	Sequence Type	**TR (ms)**	**TE (ms)**	**TI (ms)**	**ETL/Turbo Factor (NEX/NSA)**	**Bandwidth**

Siemens 1.5T	2D TSE-IR	9000–9820	66–87	2500	9 (1)	110 Hz/px
Siemens 3T	2D TSE-IR	9400	75–85	2500	9 (1)	201 Hz/px
GE 1.5T	2D T2-FLAIR	9000	80–92	2250	- (1)	15.6 kHz
GE 3T	2D T2-FLAIR	9000	80–92	2200–2500	- (1)	31.25 kHz
Philips 1.5T	2D Turbo FLAIR	9000	80	2500	9–12 (1)	Water-fat shift=2
Philips 3T	2D Turbo FLAIR	9000	80	2500	12 (1)	Water-fat shift=3
Toshiba 1.5T	2D FSE+13.5_n BW_slt(15)	10000	107	2200	15 (1)	-
Other models	2D Turbo FLAIR	6810–9910	66–90	2200	8 (1)	110 Hz/px

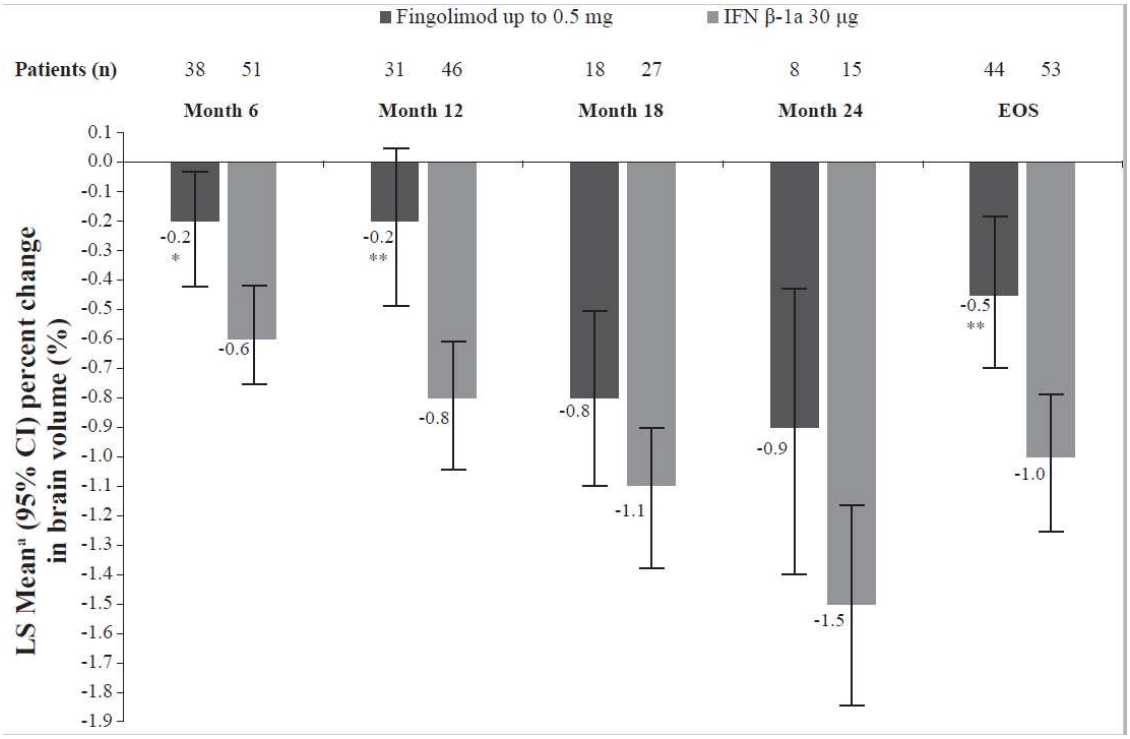
2D, two-dimensional; 3D, three-dimensional; BW, bandwidth D, dimensional; ET, echo time; ETL, echo train length; FLAIR, Flow sensitive Alternating Inversion Recovery; FFE, fast field-echo; FLAIR, Fluid-attenuated inversion recovery; FSE, fast spin echo; Hz/px, hertz/pixel; IR, inversion recovery; NEX, Number of Excitations; NSA, Number of Signal Averages; PDW, Proton Density-weighted; R-L, right-left; SPGR, spoiled gradient recalled; SPGR, spoiled gradient recalled; T1W, T1-weighted; T2W, T2-weighted sequence; TE, echo time; TI, inversion time; TR, repetition time; TSE, turbo spin echo

Figure S1. Box and whiskers plot of ARBA (re-baselined from Month 6) at EOS (FAS)



ARBA, Annualized rate of brain atrophy; EOS, end of study; FAS, full analysis set; IFN, interferon

Figure S2. Percent change in brain volume from baseline by time point in patients with no Gd+ lesions at baseline (FAS)



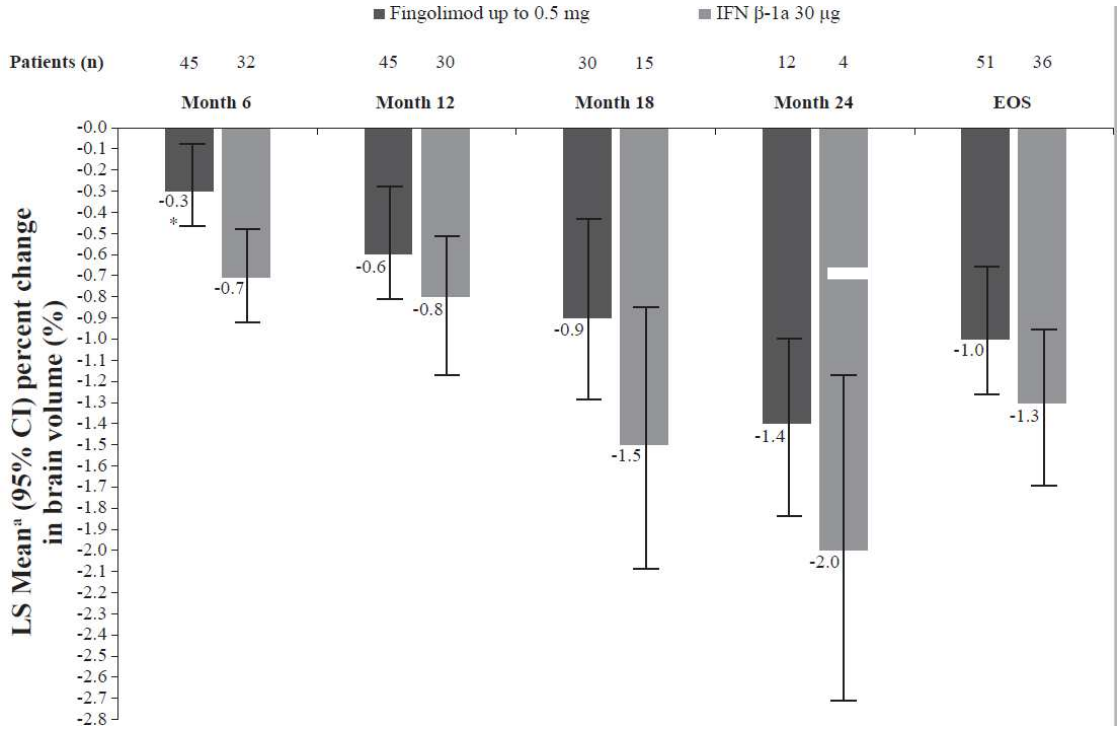
**p≤0.05 vs IFN β-1a; **p≤0.001 vs IFN β-1a*

Data are expressed as adjusted mean±95% CI. n, number of patients included in each analysis. EOS is defined as the last assessment taken on or before the final study phase visit date.

[a]Obtained from fitting an ANCOVA model adjusted for treatment, region, pubertal status (the stratification factor in IVRS), and baseline normalized brain volume as covariates.

ANCOVA, analysis of covariance; EOS, end of study; CI, confidence interval; FAS, full analysis set; IFN, interferon; Gd+, gadolinium-enhancing; IVRS, Interactive Voice Response System; LS, least square

Figure S3. Percent change in brain volume from baseline by time point in patients with ≥1 Gd+ lesions at baseline (FAS)



**p≤0.05 vs IFN β-1a*

Data are expressed as adjusted mean±95% CI. n, number of patients included in each analysis. EOS is defined as the last assessment taken on or before the final study phase visit date.

[a]Obtained from fitting an ANCOVA model adjusted for treatment, region, pubertal status (the stratification factor in IVRS), and baseline normalized brain volume as covariates.

ANCOVA, analysis of covariance; EOS, end of the study; CI, confidence interval; FAS, full analysis set; IFN, interferon; Gd+, gadolinium-enhancing; IVRS, Interactive Voice Response System; LS, least square