**Supplemental material 1**

**Inclusion and exclusion criteria**

**Inclusion criteria**

* Age 18 to 65 years
* PPMS according to the McDonald (2010) and Lublin (2014) criteria1,2
* Disease duration at least one year
* EDSS ≤6.5
* Written informed consent
* No other signs of significant disease judged by the investigator
* Eligible for randomisation to active treatment or placebo as assessed by CSF NFL levels above 380 ng/l
* Patients not eligible for randomisation due to low NFL concentrations in CSF at screening can be followed up after 48 weeks, and are eligible for open-label treatment if they fulfil one of the following clinical criteria of disease progression:
	+ 1 point increase in EDSS score from screening to week 48 if screening EDSS <6
	+ 0.5 point increase in EDSS score from screening to week 48 if screening EDSS>5.5
	+ 2 point increase in a physical functional system
	+ Worsening in SDMT, 9HPT or T25FW >20% from screening to week 48

**Exclusion criteria**

* Pregnancy or breastfeeding
* Lack of effective contraception for women of childbearing potential
* Relapse within 6 months of inclusion
* Methylprednisolone treatment within 3 months of inclusion
* Treatment with interferon-beta, glatiramer acetate, immunoglobulin G or other immunomodulatory treatment within 6 months of inclusion
* Treatment with mitoxantrone, cyclophosphamide, azathioprine or other immunosuppressive treatment within 6 months of inclusion
* Findings on the screening magnetic resonance imaging (MRI) judged to preclude participation by the treating physician
* Other diseases associated with immunodeficiency
* Other diseases judged to be relevant by the treating physician
* Anticoagulant therapy other than platelet inhibitors
* Active malignant disease in the previous 5 years
* Renal insufficiency or blood creatinine > 150 μmol/l
* Present or chronic infection with hepatitis B virus, hepatitis C virus, HIV (tested in the screening blood samples) or other infections found to be relevant by the treating physician
* Psychiatric disorders or other disorders impairing the patient’s ability to participate in the trial
* Contraindication to MRI
* Known allergy or hypersensitivity to dimethyl fumarate

**Primary, secondary and tertiary endpoints**

**Primary endpoint**

* Difference in change in the CSF concentration of NFL from screening to week 48 in PPMS patients treated with dimethyl fumarate or placebo

**Secondary endpoints**

* CSF endpoints: comparison of change from screening to week 48 in patients treated with dimethyl fumarate and placebo for the following variables:
	+ - * + Concentrations of: MBP, sCD27, sBCMA, CHI3L1 and sCD14
				+ IgG-index
				+ CSF-serum albumin quotient
* MRI endpoints: comparison of change from screening to week 48 in patients treated with dimethyl fumarate and placebo for the following variables:
	+ - * + Number of new or enlarged T2 lesions
				+ Fractional anisotropy (FA) in normal appearing white matter (NAWM)
				+ Lesion volume
				+ Magnetization Transfer Ratio (MTR) in lesions
				+ Thalamic volume
				+ Percentage brain volume change (PBVC)
* Clinical endpoints: comparison of change from screening to week 48 in patients treated with dimethyl fumarate and placebo for the following variables:
	+ - * + Expanded Disability Status Scale (EDSS)
				+ Timed 25-Foot Walk (T25FW)
				+ Nine-Hole Peg Test (9HPT)
				+ Brief International Cognitive Assessment for MS (BICAMS)

Symbol Digit Modalities Test (SDMT)

**Tertiary endpoints**

* MRI endpoints: comparison of change from screening to week 48 in patients treated with dimethyl fumarate and placebo for the following variables:
	+ - * + Number of Gd enhancing lesions
				+ Total number of lesions
				+ Volume of Cortical Grey Matter (CGM), NAWM and the putamen nuclei
				+ Change in MTR of CGM, NAWM, the putamen and thalamic nuclei
				+ Change in diffusion tensor imaging (DTI) measures (FA and mean diffusivity) of CGM, NAWM (except FA in NAWM), lesions, the putamen and thalamic nuclei
				+ Cross sectional area at C2 level of the cervical spinal cord
* Clinical endpoints: comparison of change from screening to week 48 in patients treated with dimethyl fumarate and placebo for the following variables:
	+ - * Brief International Cognitive Assessment for MS (BICAMS)
		- Brief Visuospatial Memory Test Revised (BVMT-R)
		- California Verbal Learning Test 2 (CVLT-II)
* Self-reported outcome measures: comparison of change from screening to week 48 in patients treated with dimethyl fumarate and placebo for the following variables:
	+ - * + Urinary Distress Inventory (UDI)
				+ Fatigue Scale for Motor and Cognitive Functions (FSMC)
				+ Multiple Sclerosis Impact Scale 29 (MSIS-29)

**References**

1. Polman CH, Reingold SC, Banwell B, Clanet M, Cohen JA, Filippi M, et al. Diagnostic criteria for multiple sclerosis: 2010 Revisions to the McDonald criteria. Ann Neurol. 2011 Feb;69(2):292–302.

2. Lublin FD, Reingold SC, Cohen JA, Cutter GR, Sørensen PS, Thompson AJ, et al. Defining the clinical course of multiple sclerosis: The 2013 revisions. Vol. 83, Neurology. 2014. p. 278–86.