eTable 1: Inclusion/exclusion criteria of the Phase 3 studies

	Inclusion criteria	**Exclusion criteria**
European Study[e14] (IFNβ-1b) (Kapoor et a_ 1998)	• Age 18–55 years • Baseline EDSS score of 3·0–6·5 inclusive and a recorded history of either two relapses or more or 1·0 point or more increase in EDSS in the previous 2 years • Clinically or laboratory supported definite diagnosis of MS • Secondary progression was defined as a period of deterioration, independent of relapses, sustained for at least 6 months, and that followed a period of relapsing-remitting MS. Superimposed relapses were allowed	• Immunosuppressive or immunomodulatory treatment and other putative treatments for MS were not permitted for defined periods before entry into the study
North American Study[15]	• Age 18 to 65 years, • Clinically definite or laboratory supported definite MS of at least 2 years' duration • History of at least one relapse followed by progressive deterioration sustained for at least 6 months • EDSS score at screening of 3.0 to 6.5 inclusive • Increase in EDSS score of at least 1.0 point in the 2 years prior to screening (at least a 0.5 point increase for subjects with a screening EDSS score of 6.5)	• Received treatment with systemic corticosteroids or adrenocorticotropic hormone within 60 days before the screening visit • Previously treated with any IFNβ, monoclonal antibody, cladribine, or total lymphoid irradiation • Received cytotoxic or immunosuppressive therapy, glatiramer acetate, or other investigational drug within 6 months before the screening visit
SPECTRIMS study [e11] (IFNβ-1b) 2001	• Age between 18 and 55 years old, with EDSS scores from 3.0 to 6.5 and pyramidal functional score of at least 2 • Clinically definite SPMS, defined as progressive deterioration of disability for at least 6 months with an increase of at least 1 • EDSS point over the last 2 years (or 0.5 point between EDSS score of 6.0 and 6.5), with or without superimposed exacerbations, following an initial RR course •	• Immunosuppressive or immunomodulatory treatments during the previous 3 to 12 months depending on the drug, prior treatment with interferon or total lymphoid irradiation, corticosteroid use or a disease exacerbation in the previous 8 weeks, severe concurrent illness, and pregnancy or lactation
IMPACT study[e12] (IFNβ-1a) (Cohen et al 2002)	• Age 18 to 60 years inclusive • Clinically definite SPMS with or without recent relapses, disease progression over the previous year, cranial MRI demonstrating lesions consistent with MS • EDSS score of 3.5 to 6.5 inclusive	• Primary progressive course • Inability to perform the component tests of the MSFC at baseline, and prior treatment with IFN

IFN beta-1a[e13] (Anderson et al_2004)	• Age 18–65 years • Diagnosis of clinically definite MS for at least 1 year, and which was classified as SPMS with an EDSS score below 7.0 • Patients had had a prior history of RRMS and had experienced progressive deterioration of disability for at least 6 months, with an increase of at least 1.0 point on the EDSS in the previous 4 years (or 0.5 points if the entry EDSS score was 6.0 or 6.5), with or without superimposed exacerbations • Patients were in a stable neurological condition for the 4 weeks preceding study day 1	• Exclusion criteria were similar to those used in previous IFNβ trials (SPECTRIMS study)[e11]
MBP8298 study[14] (Freedman et al_2011)	• Age 18–65 years • Documented history of SPMS, absence of relapse in the 3 months leading up to trial participation, EDSS score of 3.5–6.5, and a Kurtzke pyramidal or cerebellar system subscore ≥3 • Patients meeting a stringent definition of SPMS (recent confirmed progression in EDSS in the absence of relapse), overseen by an independent adjudication committee.	• Diagnosis of PPMS, previous treatment with MBP8298 • History of malignancy • Steroid therapy within 30 days of study entry • Treatment with IFNβ, glatiramer acetate within 3 months, or mitoxantrone, cyclophosphamide, methotrexate, azathioprine, or any other immunomodulating or immunosuppressive drugs or plasma exchange within 6 months prior to the first study-specific test, with the exception of corticosteroids or ACTH for relapse
EXPAND (Siponimod) (Kappos et al_2018)[e10]	• Age 18–60 years, a diagnosis of SPMS, documented moderate-to-advanced disability indicated by an EDSS score of 3·0–6·5 at screening • A history of RRMS (2010 McDonald criteria), documented EDSS progression in the 2 years before the study, and no evidence of relapse in the 3 months before randomization	• Substantial immunological, cardiac, or pulmonary conditions, ongoing macular oedema, uncontrolled diabetes, CYP2C9*3/*3 genotype, and varicella zoster virus antibody negative status
ASCEND[11] (Natalizumab) (Kapoor et al_2018)	• Natalizumab-naive patients aged 18–58 years were eligible for enrolment in part 1 of the ASCEND study if they had onset of SPMS 2 or more years before enrolment, an EDSS score of 3·0–6·5 (inclusive), a Multiple Sclerosis Severity Score of 4 or more, and disability progression not related to clinical relapses during the year before enrolment,	• Patients who had a clinical relapse up to 3 months before randomization (to prevent recent relapses from influencing the baseline • Patients were excluded from part 2 if they had discontinued study treatment, received less than 20 infusions, or missed two or more consecutive infusions in part 1

	as assessed by clinical historical findings with a standardized form • For inclusion in part 2, eligible patients were required to have participated in part 1 and to have completed all part 1 examinations and efficacy assessments before receiving the first open-label dose at week 108 in part 2	
SPI (MD-1003)[13] (Cree et al_2020)	• Age 18–65 years • Diagnosis of primary or SPMS fulfilling the revised International Panel criteria (2010) and Lublin criteria (2014); Kurtzke pyramidal functional subscore of at least 2, defined as minimal disability; TW25 less than 40 at screening visit; EDSS score 3·5–6·5; and documented evidence of clinical disability progression in the 2 years before enrolment, as defined by ➢ worsening of EDSS of at least 1 point (EDSS 3·5–5·5) or at least 0·5 points (EDSS 6–6·5), sustained for at least 6 months; ➢ increase of TW25 by at least 20% in the past 2 years sustained for at least 6 months; or • other well documented objective worsening confirmed by an independent clinical adjudication committee	• Key exclusion criteria were: ➢ clinical evidence of a relapse in the 2 years before inclusion and • concomitant treatment with fampridine in the 30 days before inclusion

Abbreviations: EDSS, Expanded Disability Status Scale; IFNβ, interferon beta; MS, multiple sclerosis; MSFC, MS Functional Composite; PPMS, primary progressive multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis; TW25, Timed 25-Foot Walk

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