Table 1: Early treatment to reduce conversion of CIS (clinically isolated syndrome) to CDMS (Clinically Definite Multiple Sclerosis): costing and QALY data from the literature (figures were inflated to 2020 values)

Country	Effectiveness data	Model of analysis	Time horizon (years)	Healthcare provider costs per person (euros)			Societal costs per person (euros)			QALY per person		
				CIS	CDMS	diff costs	CIS	CDMS	diff costs	CIS	CDMS	diff QALY
Italy (Lazzaro C, et al. 2009)	Trial: BENEFIT	Epidemiological	25	207,217	206,314	903	268,702	275,537	-6,834	7.84	7.49	0.35
Spain (Piñol C. 2016)	Trial: BENEFIT	Markov	50	386,310	354,632	31,678	680,964	691,404	-10,441	15.42	14.68	0.74
Sweden (Fredrikson S, et al. 2013)	Trial: REFLEX	Markov	40				853,855	883,706	-29,851	13.79	13.26	0.53

Note: The trials assessed the impact of IFN-1b treatment after CIS (early treatment) compared with the impact of delaying IFN-1b treatment until diagnosis of CDMS (delayed treatment).

Table 2. Early treatment to reduce conversion of CIS (clinically isolated syndrome) to CDMS (Clinically Definite Multiple Sclerosis): clinical and health outcomes

Outcomes	Comparison group		Results
	Intervention	**Comparison**	
Conversion to CDMS	Oral cladribine 5,25 mg/kg (G1) and 3,25 mg/kg(G2) (Leist TP, et al. 2014)	Placebo	Gain in risk conversion: from 33.4% (96 weeks) to 33% (11 years)
	IFN-1b (Kappos L, et al. 2006)		
Time to conversion	Oral cladribine 5,25 mg/kg (G1) and 3,25 mg/kg(G2) (Leist TP, et al. 2014)	Placebo	Gain in time to conversion: from 344 days (96 weeks) to 363 (2 years)
Cognitive performance	IFN-1b (Penner IK, et al. 2012)	Placebo	Gain in mean PASAT-3 score: 1.9
Level of disability	IFN-1b (Kappos L, et al. 2006)	Placebo	69.8% has an EDSS score lower than 3.0
MRI outcomes	IFN-1b (De Stefano N, et al. 2014)	Placebo	37-57% reduction in new T1 hypointense lesions
			76-92% reduction in new T1 Gd+ lesions
			57-70% reduction in new T2 lesions
Quality of life	IFN-1b (Kappos L, et al. 2006)	Placebo	Gain in PASAT-3 score: 0.9

Table 3: Decision analytic models for smoking cessation and 25 hydroxy vitamin D (25(OH)D) serum levels on MS worsening

(a) Smoking cessation		Alternative 1 Ever smokers (n=1000 MS cases)				Alternative 2 Non-smokers (i.e., never smoked) (n=1000 MS cases)			Outcomes
		EDSS I	EDSS II	EDSS III		EDSS I	EDSS II	EDSS III	
Baseline scenario	MS patients (HR = 1.55) Hempel S, et al. 2017(a))	330	280	390	MS patients (Kobelt G&Pugliatti M, 2005)	570	220	210	Annual (direct and indirect) costs; QALYs; see Figure 1
Sensitivity 1	MS patients (HR = 1.10) Hempel S, et al. 2017(a))	570	180	250	MS patients (Kobelt G&Pugliatti M, 2005)	570	220	210	
Sensitivity 2	MS patients (HR = 2.19) Hempel S, et al. 2017(a))	240	240	510	MS patients (Kobelt G&Pugliatti M, 2005)	570	220	210	

(b) 25(OH)D serum levels		Alternative 1 No increased level of serum 25(OH)D (n=1000 MS cases)				Alternative 2 Increased level of level of serum (25(OH)D)[a] (n=1000 MS cases)			Outcomes
		EDSS I	EDSS II	EDSS III		EDSS I	EDSS II	EDSS III	
Baseline scenario	MS patients (Kobelt G&Pugliatti M, 2005)	570	220	210	MS patients (SMD = -0.22) Hempel S, et al. 2017(a))	717	253	30	Annual (direct and indirect) costs; QALYs; see Figure 1

Sensitivity 1	MS patients (Kobelt G&Pugliatti M, 2005)	570	220	210	MS patients (SMD = -0.32) Hempel S, et al. 2017(a))	820	180	0
Sensitivity 2	MS patients (Kobelt G&Pugliatti M, 2005)	570	220	210	MS patients (SMD = -0.12) Hempel S, et al. 2017(a))	643	267	90

HR = Hazard Ratio; SMD = Standardised Mean Difference; [a] from <20 mmol/l to 20+ mmol/l