



Reducing the Burden of MS Treatment: Meeting the Unmet Need

gmsa
Global Multiple
Sclerosis Academy

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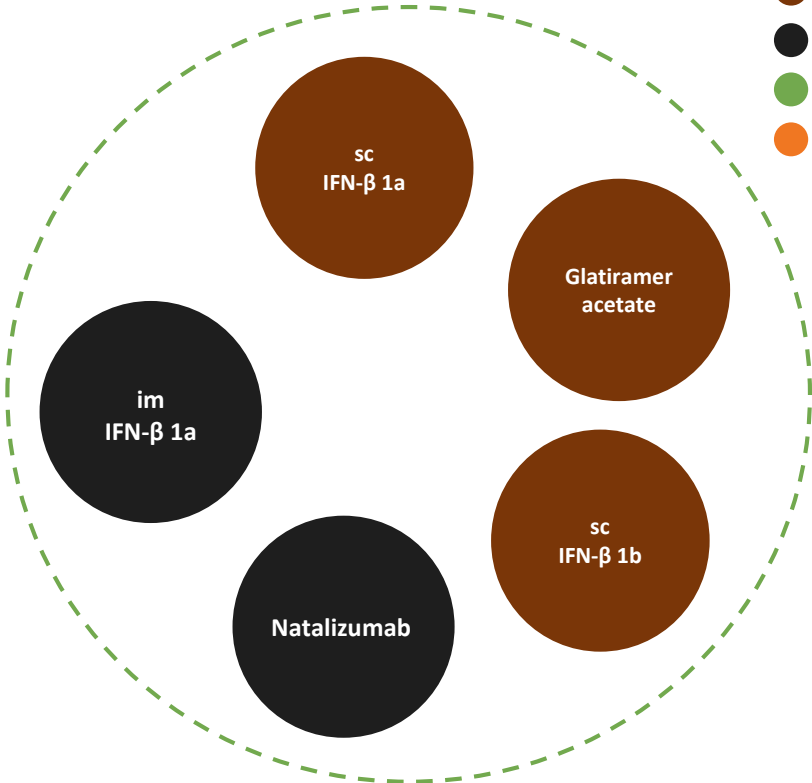
Learning Objectives

- a. Review the benefit/risk strategies in selecting therapy for MS patients while assessing potential treatment regimens that carry acceptable or diminished risk of disease progression**
- b. Explore emergent concepts in the management of MS, focusing on targeting T- and B-cells including:**
 - Risks associated with continuous immunosuppression
 - Action on the inflammatory activity in the CNS compartment
- c. Identify strategies that simplify patient dosing and side effects to:**
 - Increase treatment compliance
 - Improve patients' quality of life
 - Slow disease progression

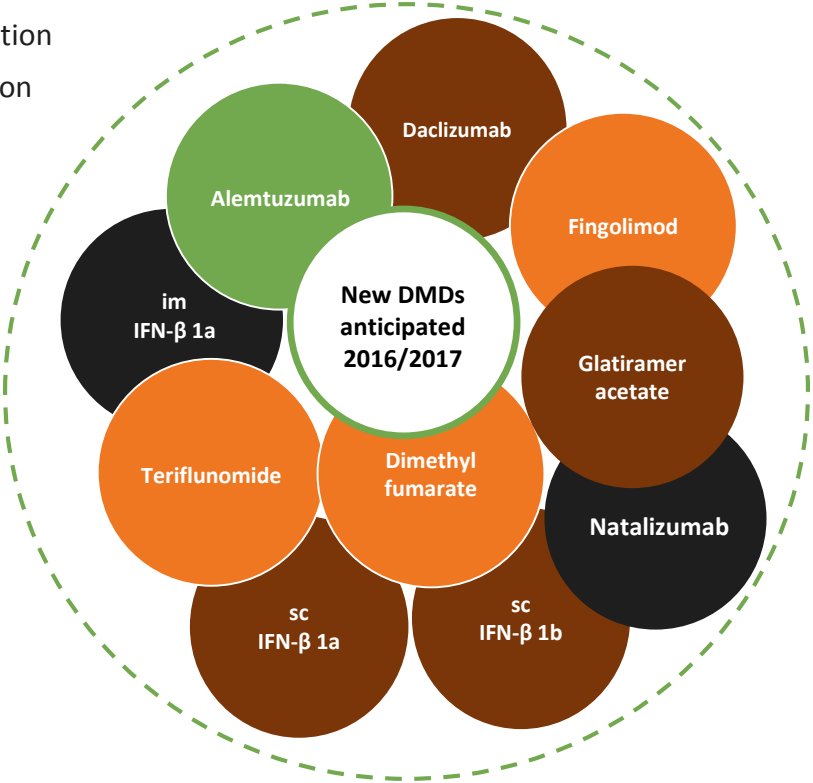
MS is the leading cause for acquired non-traumatic neurological disability in young adults.

Therapeutic Options in Europe have Doubled in the Last 6 Years

Licensed therapies available in Europe in 2010



Licensed therapies available in Europe in 2016



Unmet Needs in MS

Further delaying progression

Providing neuroprotection

Delaying or avoiding disability

Optimising brain health

Reducing active symptoms more effectively

Identifying useful tools and biomarkers

Individualized treatment

Reducing monitoring requirements

Better measures of functional outcome

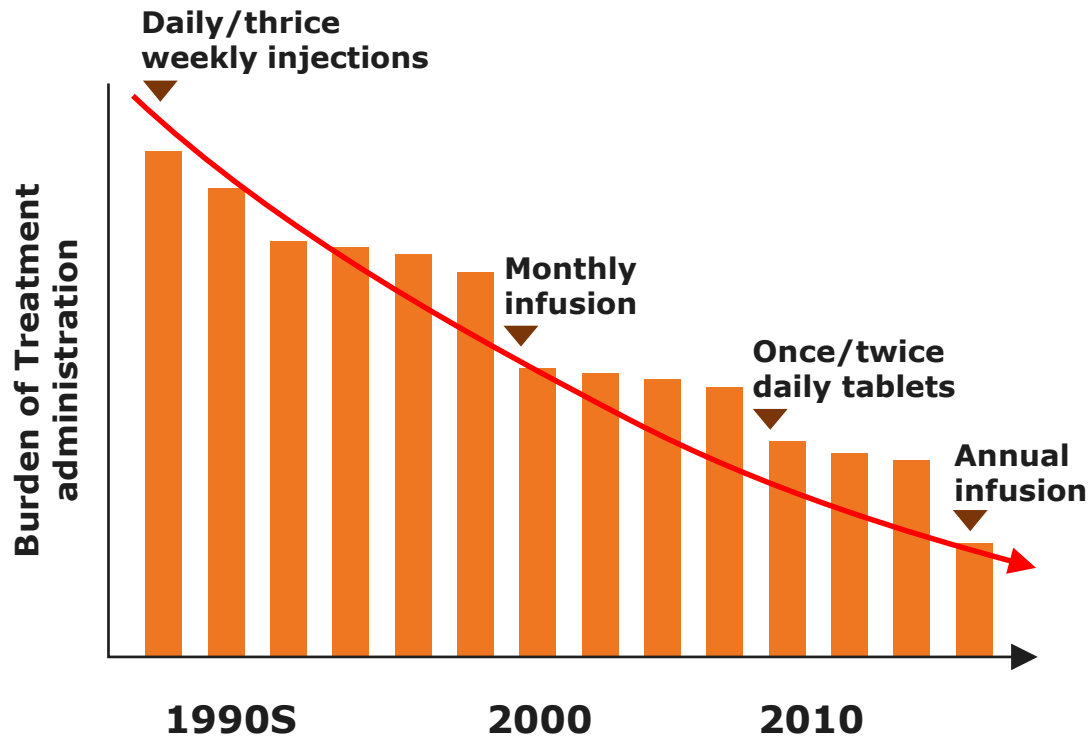
Improving adherence to current medications

Preventing or reducing the adverse effects of current medications

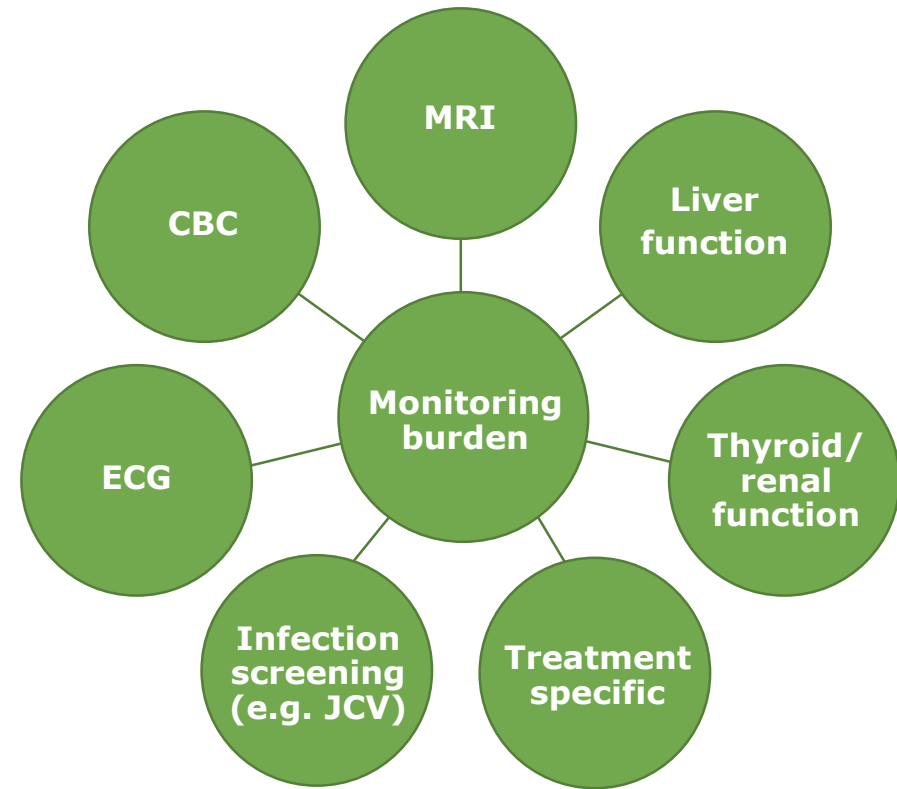
Limit effects of Immuno-suppression

Treatment Burden has Improved – Monitoring Burden Has Increased

While the burden of administration with MS therapies has decreased over time...¹



...this has been accompanied by an increase in monitoring burden^{2,3}



1. Ransohoff RM et al. *Nat Rev Neurol* 2015;11:134-142. 2. Rommer PS et al. *Clin Exp Immunol.* 2014;175:397-.407. 3. Ziemssen T et al. *J Neurol.* 2016;263:1053-1065.

MS Treatment and Management Burden

Treatment

The burden of MS treatment is substantial¹⁻³

- There is no cure for MS so lifelong treatment is required
- Most DMDs have low treatment tolerability with frequent administration and high incidence of side effects

A therapy with a low treatment burden would require

- ✓ Fewer administrations
- ✓ Convenient dosing
- ✓ Fewer clinic visits

Management

Current DMDs have a substantial monitoring burden and require frequent clinic visits^{2,3}

- Pre-treatment preparation
- First-dose monitoring
- On-going monitoring and vigilance

A therapy with a low management burden would require

- ✓ Less co-medication
- ✓ Less monitoring
- ✓ Simplified clinical data interpretation

DMD, disease-modifying drug

1. Mehr SR et al. *Am Health Drug Benefits*. 2015;8:426-431. **2.** Clanet MC et al. *Mult Scler*. 2014;20:1306-1311. **3.** Rommer PS et al. *Clin Exp Immunol*. 2014;175:397-407; **4.** Steinberg SC et al. *Clin Drug Invest* 2010;30:89-100; **5.** Bayas A et al. *Expert Opin. Drug Deliv*. 2015;12:1239-1250.

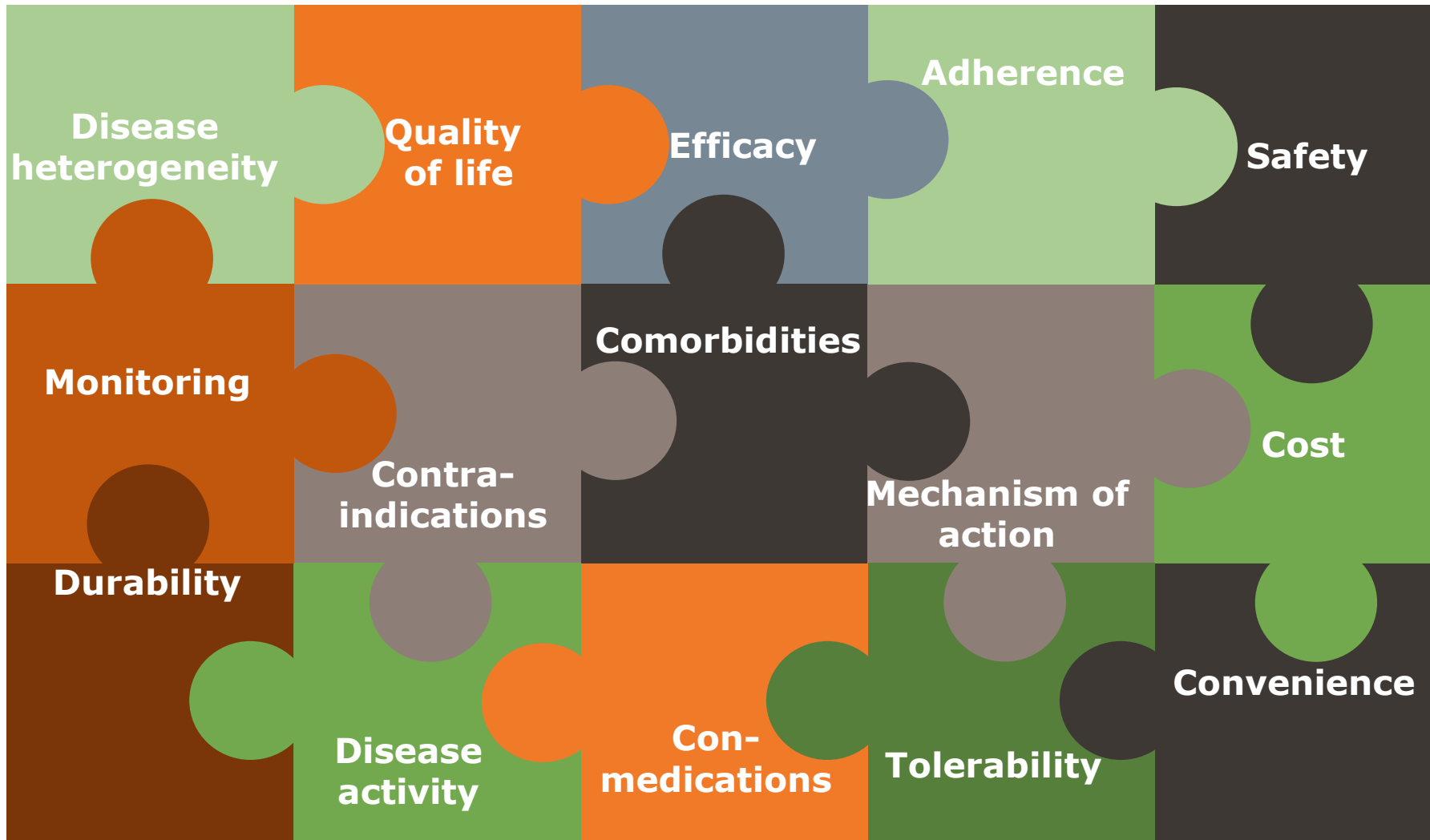
Platform Therapies Have A Relatively Low Burden Of Monitoring

	EU and US labels	EU label only	US label only						
Monitoring Requirement	sc IFN β -1a ^{1,2}	im IFN β -1a ^{1,2}	Glatiramer acetate ^{2,3}	Teriflunomide ^{1,2}	Dimethyl fumarate ^{1,2}	Fingolimod ^{1,2}	Natalizumab ^{1,2}	Alemtuzumab ^{1,2}	Daclizumab ^{1,2}
Black triangle for additional monitoring (EU label)									
				▼		▼	▼	▼	▼
Infections				✓		✓	✓	✓	✓
Lymphopenia					✓	✓			
Liver function	✓	✓		✓		✓			✓
Blood counts/ chemistry	✓	✓		✓	✓	✓		✓	✓
Blood pressure				✓	✓	✓			
Renal function								✓	
PML					✓	✓	✓		
Ophthalmology						✓			
Administration route	Injection	Injection	Injection	Oral	Oral	Oral	Infusion	Infusion	Injection
Number of administrations over 1 year ^b	156	52	365	365	730	365	12	5	12

EU and US labels accessed August 2016. aIn patients with existing impairment and/or as clinically indicated. PML, progressive multifocal leukoencephalopathy. bCalculated from the frequency of administration approved in the product labels. IFN, interferon; im, intramuscular; sc, subcutaneous

1. EU Summary of Product Characteristics. 2. US Prescribing Information. 3. Copaxone® UK Summary of Product Characteristics.

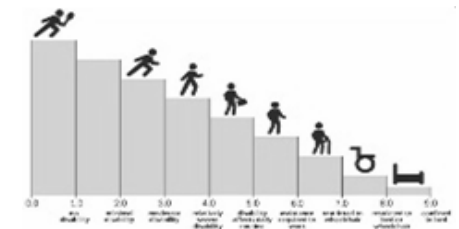
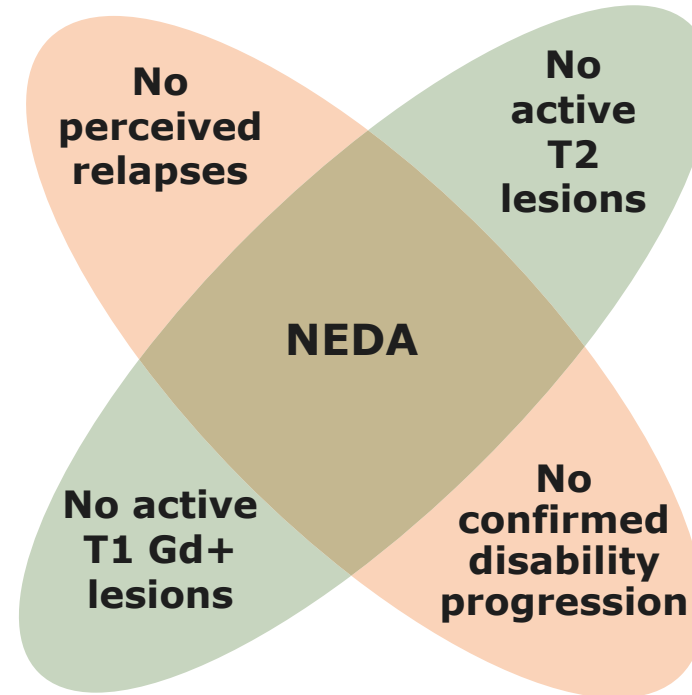
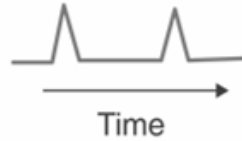
Several factors impact MS treatment decisions



Brück W et al. *JAMA Neurol.* 2013;70:1315–1324. Freedman MS et al. *Can J Neurol Sci.* 2004;3:157–168. Wingerchuk and Carter. *Mayo Clin Proc.* 2014;89:225–240.

New Pretreatment Paradigm – Treat-2-Target

Treating to achieve NEDA is an emerging treatment paradigm in the management of patients with RMS



NEDA is based on the principle that relapse rates, disability progression and MRI activity are not independent¹⁻³

Gd+, gadolinium-enhancing; MRI, magnetic resonance imaging; NEDA, no evidence of disease activity; RMS, relapsing MS.

1. Bevan CJ, Cree BA. *JAMA*. 2014;71:269-270. 2. Sormani MP et al. *Mult Scler*. 2011;17:541-549. 3. Kappos L et al. *Mult Scler J*. 2016;22:1297-1305.

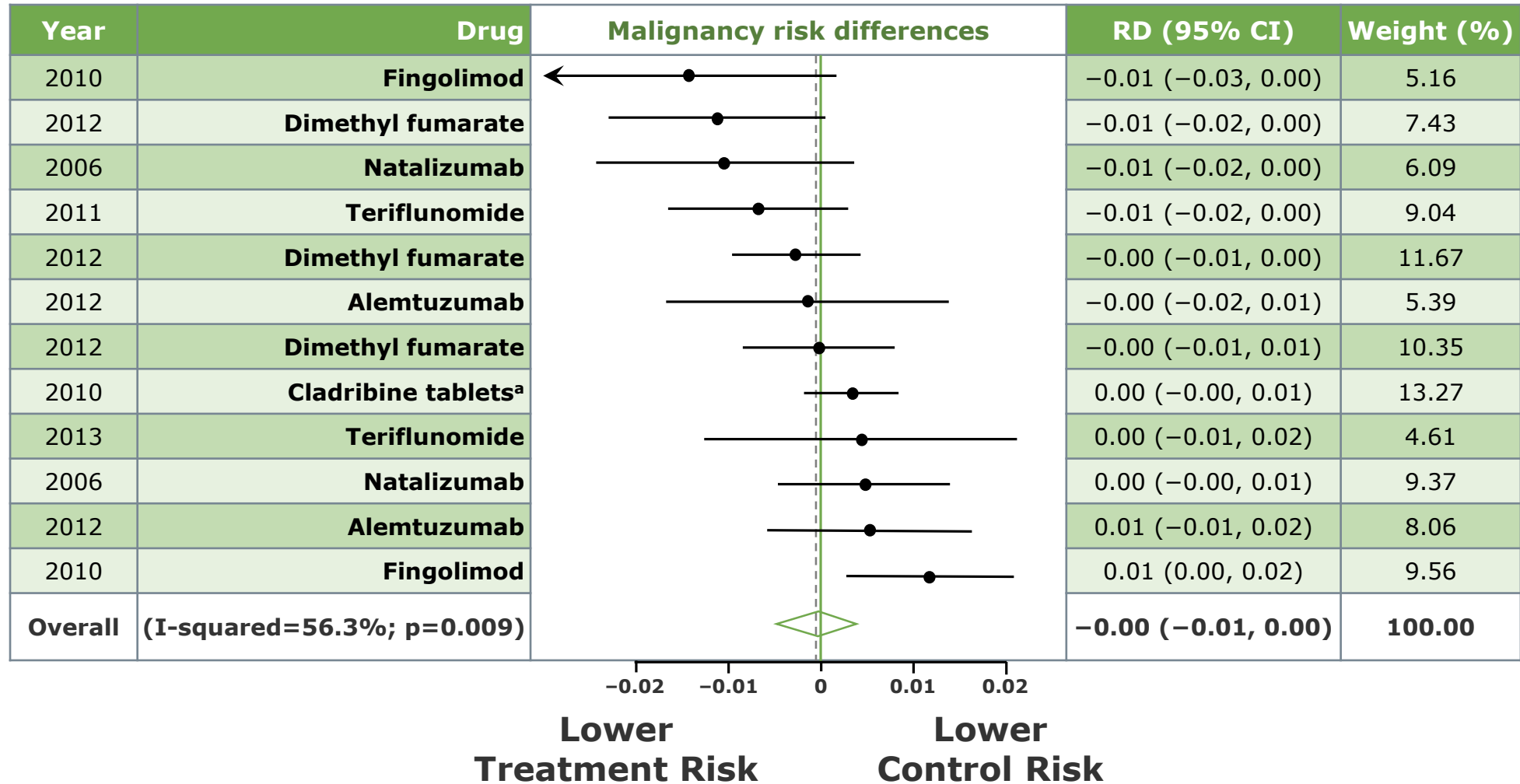
Risks Associated with Prolonged or Continuous Immunosuppression

T cells and B cells play critical roles in MS, and therapies targeting lymphocytes have a clinical effect¹

Nature of immunosuppression ²	Likely infectious agents ²
Neutrophil deficits	Bacteria
	Fungi
Abnormal T cells or monocytes	Viruses
	Parasites
	Fungi (typically yeast forming)
	Bacteria
Disorders of humoral immunity ³	Bacteria

1. McFarland HF et al. *Nat Immunol.* 2007;8:913–919; **2.** Nath A, Berger JR. *Curr Treat Options Neurol.* 2012;14:241–255. **3.** Winkelmann A et al. *Clin Exp Immunol.* 2014;175:425–438.

Malignancy Risk Among MS Treatments



Note: Weights are from random effects analysis.

Risks Associated With Continuous Immunosuppression

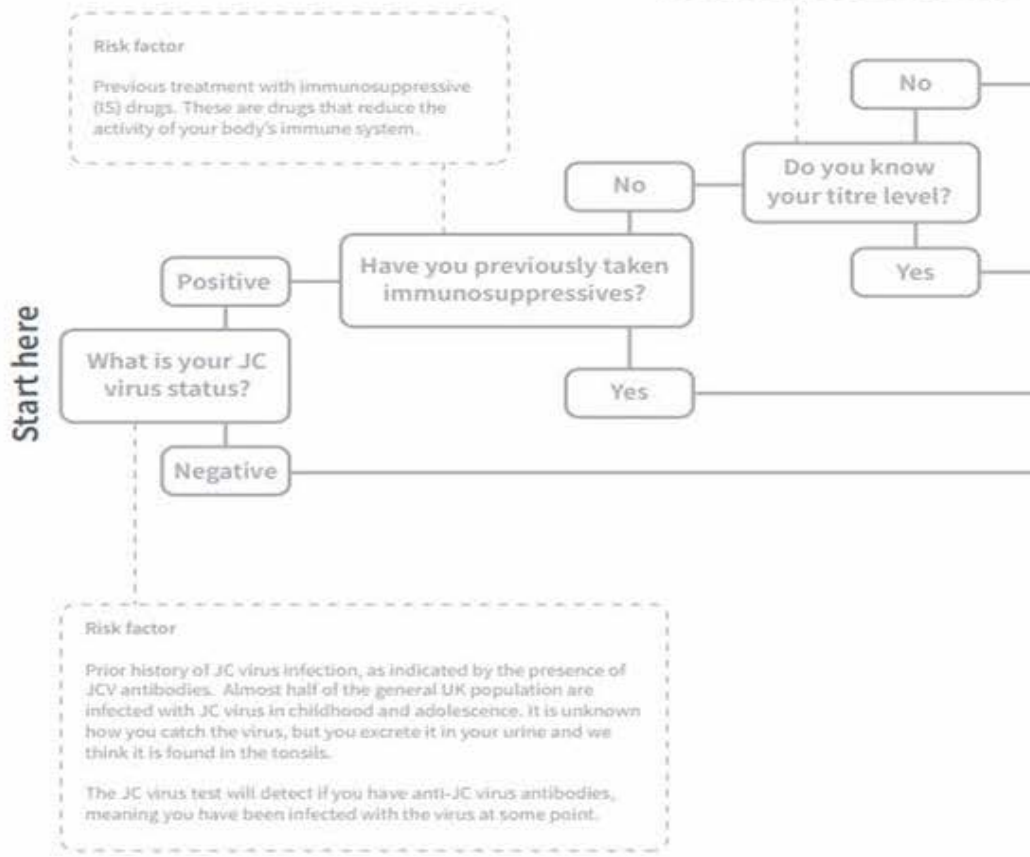
		RISKS ASSOCIATED WITH IMMUNOSUPPRESSION		
		OPPORTUNISTIC INFECTIONS EXCEPT PML	PML	CANCER
sc IFN β 1a ¹		Not stated in SmPC	Not stated in SmPC	Not stated in SmPC
Glatiramer acetate ²		Not stated in SPC	Not stated in SPC	Yes (skin cancer)
Teriflunomide ³	EU	Not stated in SmPC	Not stated in SmPC	No evidence of increased risk
Dimethyl fumarate ⁴		Not stated in SmPC	Warning included in SmPC	Not stated in SmPC
Natalizumab ⁵	EU	Yes (herpes simplex/varicella zoster encephalitis/meningitis)	Warning included in SmPC	Not established
Fingolimod ⁶	EU	Yes (varicella zoster/HSV/cryptococcal meningitis)	Warning included in SmPC	Yes (basal cell carcinoma)
Alemtuzumab ⁷	EU	Yes (varicella zoster/ cervical HPV/tuberculosis)	Not stated in SmPC	Not established (possible risk of thyroid cancer)
Daclizumab ⁸	EU	Yes (pneumonia, tuberculosis)	NR	NR
Cladribine tablets ^{a,9}		Yes (herpes zoster)	NR	SIR 0.99 ¹⁰
Ocrelizumab ^a		NR	NR	11 cases/486 patients ¹¹ 4 cases/852 patients ¹²

^aThese agents are under clinical investigation and have not been proven to be safe and effective. There is no guarantee they will be approved in the sought-after indication. EU = EU label: Medicine is under additional monitoring. HPV, human papillomavirus; HSV, herpes simplex virus; IFN, interferon; NR, not reported; PML, progressive multifocal leukoencephalopathy; sc, subcutaneous; SIR, standardized incidence ratio; SmPC, Summary of Product Characteristics.

1. Rebif® EU SmPC; **2.** Copaxone® UK PI; **3.** Aubagio® EU SmPC; **4.** Tecfidera® EU SmPC; **5.** Tysabri® EU SmPC; **6.** Gilenya® EU SmPC; **7.** Lemtrada® EU SmPC; **8.** Zinbryta® EU SmPC; **9.** Giovannoni G, et al. *N Engl J Med.* 2010;362:416–426; **10.** Cook S et al. *Mult Scler.* 2011;17:578–593; **11.** ORATORIO Montalban X et al. *Neurology.* 2016;86(Suppl 16):S49.001; **12.** OPERA I and II: Hauser SL et al. *Neurology.* 2016;86(Suppl 16). EU and US labels accessed August 2016.

PML Risk Varies over Time with Natalizumab

What is your risk of developing PML?



Risk factor
Previous treatment with immunosuppressive (IS) drugs. These are drugs that reduce the activity of your body's immune system.

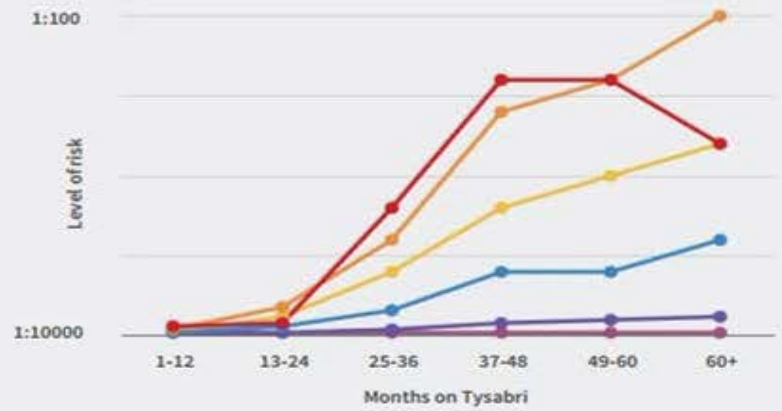
Risk factor
Your risk increases with a higher titre level. This is the level of antibodies in your blood.

Risk factor
Prior history of JC virus infection, as indicated by the presence of JCV antibodies. Almost half of the general UK population are infected with JC virus in childhood and adolescence. It is unknown how you catch the virus, but you excrete it in your urine and we think it is found in the tonsils.

The JC virus test will detect if you have anti-JC virus antibodies, meaning you have been infected with the virus at some point.

PML risk over time

	Months on Tysabri					
	1-12	13-24	25-36	37-48	49-60	60+
No index	1 in 10000	1 in 1567	1 in 500	1 in 250	1 in 200	1 in 167
More than 1.5	1 in 5000	1 in 1111	1 in 333	1 in 143	1 in 125	1 in 100
Between 0.9-1.5	1 in 10000	1 in 3333	1 in 1250	1 in 500	1 in 500	1 in 333
Less than 0.9	1 in 10000	1 in 10000	1 in 5000	1 in 2500	1 in 2000	1 in 1667
Prior use of IS	1 in 3333	1 in 2500	1 in 250	1 in 125	1 in 125	1 in 167
JCV Negative	1 in 10000	1 in 10000	1 in 10000	1 in 10000	1 in 10000	1 in 10000



Alemtuzumab Risk Management Strategy

Risks	Labelling	Education	Laboratory tests	PASS
Identified				
IARs	Posology Prophylaxis (steroids) & symptomatic treatment (anti-histamines/anti-pyretics) Cardiac history Resources to manage serious reactions			☑
Serious Infection	Posology Prophylaxis (anti-herpes agent) Contraindication HIV Warning & Precautions Active infections, concomitant immunosuppression, vaccination	☑	Pap smear TB screening HBV/HCV screening Varicella screening	☑
Auto-immune	Warning & Precautions Pre-existing autoimmune conditions			
Thyroid Disorders	Warning & Precautions Signs & symptoms, need for monitoring Guidance on re-treatment in presence of thyroid disease	☑	Quarterly (TSH)	☑
ITP	Warning & Precautions Signs & symptoms, need for monitoring	☑	Monthly CBC	☑
Glomerulonephritis	Warning & Precautions Signs & symptoms, need for monitoring	☑	Monthly urine and creatinine	☑
Potential				
Cytopenia	Warning & Precautions		Monthly CBC	☑
Malignancies	Warning & Precautions - Pre-existing & ongoing conditions			☑

Skin Rash and Angioedema



Modified Protocol

Alemtuzumab Prescription for Multiple Sclerosis

Name									
Hospital no.						Consultant			
DOB						Allergies			
Pregnancy Status						Course			
	Date (repeated daily for five days for course 1 and for 3 days in course 2)	Drug/ infusion	Route	Dose (mg)	Duration	Prescribers Signature and date	Given by (nurse)	Start/ Finish time	Pharmacy
1		Alemtuzumab in 100ml sodium chloride 0.9%	iv infusion	12mg	2 hours		/	/	
2		Alemtuzumab in 100ml sodium chloride 0.9%	iv infusion	12mg	2 hours		/	/	
3		Alemtuzumab in 100ml sodium chloride 0.9%	iv infusion	12mg	2 hours		/	/	
4		Alemtuzumab in 100ml sodium chloride 0.9%	iv infusion	12mg	2 hours		/	/	
5		Alemtuzumab in 100ml sodium chloride 0.9%	iv infusion	12mg	2 hours		/	/	














































































Administer prior to each dose

Drug	Route	Dose	Frequency	Prescribers Signature and date	Pharmacy
Prednisolone	oral	100mg	Night before infusion		
Prednisolone	IVI	500mg	Hour before each infusion		
Lansoprazole	oral	15mg	Once a day for seven days (only if patient is not taking any PPI)		
Chlorphenamine injection 10mg/ml	im or slow iv	10mg	30 minutes prior to infusion		
Aciclovir	oral	200mg	Four times a day for 4 weeks		
Or Valaciclovir	oral	500mg	Twice a day for 4 weeks		
Or Famciclovir	Oral	250mg	Twice a day for 4 weeks		

Written by: Joela Mathews - Highly Specialist Pharmacist- Neurology
Approved by:

Date: August 2014
Review Date: August 2016

Monitoring Varies by Drug and Duration of Therapy

	Pre-dose	First dose	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Month 7	Month 8	Month 9	Month 10	Month 11	Month 12
IFN β-1a			 X2		 X2			 X2						
Glatiramer acetate²			Renal function and cardiac function to be monitored in cases of renal impairment and pre-existing cardiac disorder, respectively											
Teriflunomide³	 X2 		 X2	 X2	 X2	 X2	 X2	 X2						
Dimethyl fumarate⁴	   X3				 X3 			 X3 						 X3 
Natalizumab⁵	  Immuno - suppression	Hypersens.												 
Fingolimod⁶	 X2 				 X2 									
Alemtuzumab⁷	  X3 TB screening	Infusion reaction	  X2	  X2	  X3	  X2	  X2	  X3	  X2	  X2	  X3	  X2	  X2	  X3
Daclizumab⁸		Vigilance for skin reactions			 X2			 X2			 X2			 X2

Numbers indicate the number of blood tests. ECG, electrocardiogram; hypersens., hypersensitivity; SmPC, Summary of Product Characteristics.

1. Rebif® EU SmPC; **2.** Copaxone® UK PI; **3.** Aubagio® EU SmPC; **5.** Tysabri® EU SmPC; **6.** Gilenya® EU SmPC; **7.** Lemtrada® EU SmPC; **8.** Zinbryta® EU SmPC.

Patient Adherence

15%–51% of patients with MS do not adhere to their treatment regimen¹¹

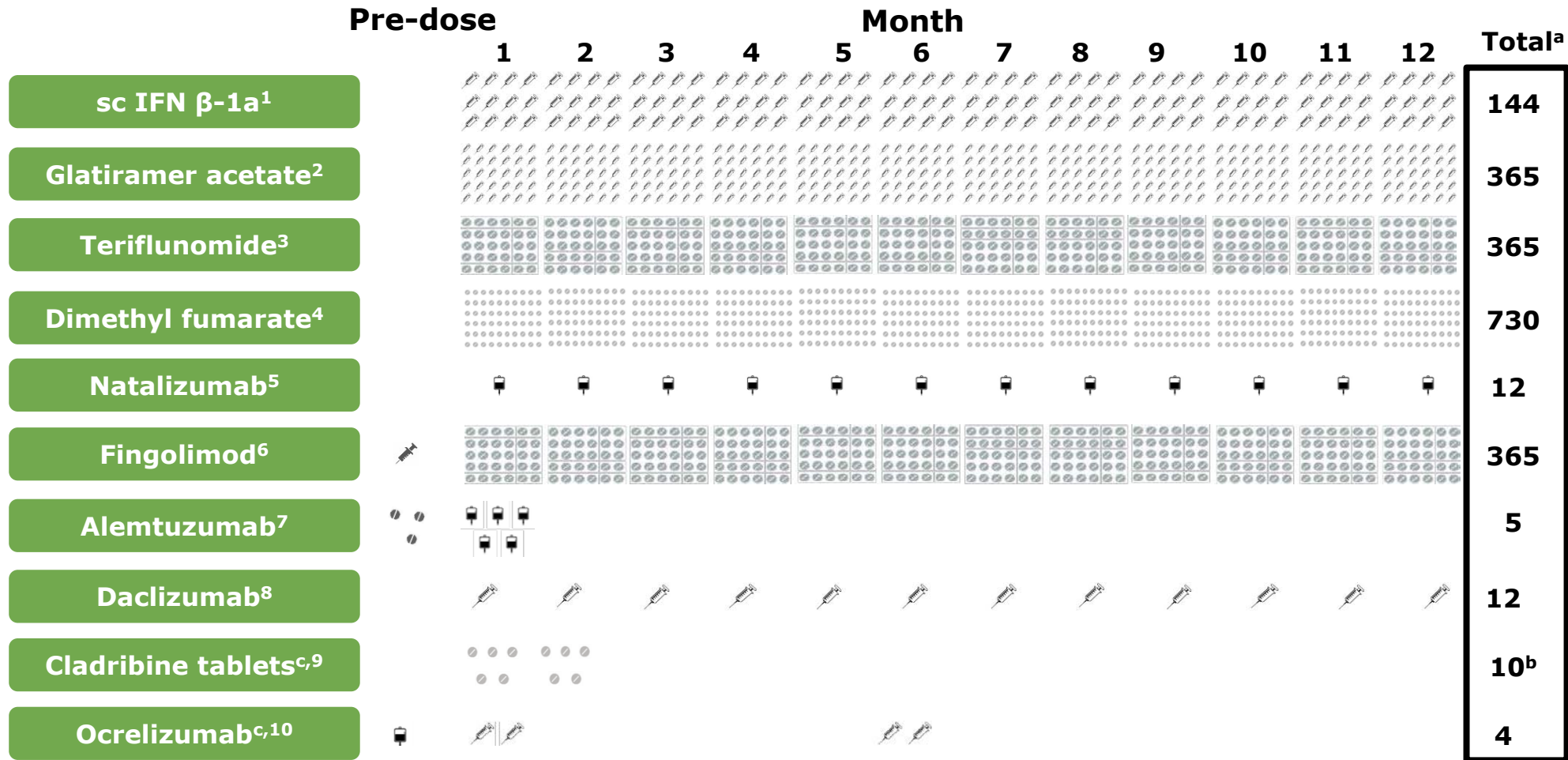
61%–96% of patients prefer an intermittent rather than once-daily treatment regimen¹²

Dose frequency is a major reason why patients with MS miss a dose¹³

^aTotal number of administrations over the first 12 months of treatment. ^b3.5 mg/kg. 5 days of treatment separated by 1 month; total number of tablets dependent on weight. ^cThese agents are under clinical investigation and have not been proven to be safe and effective. There is no guarantee they will be approved in the sought-after indication. IFN, interferon; sc, subcutaneous; SmPC, Summary of Product Characteristics.

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Treatment Frequency Varies by Drug—May Impact Adherence



^aTotal number of administrations over the first 12 months of treatment. ^b3.5 mg/kg. 5 days of treatment separated by 1 month; total number of tablets dependent on weight. ^cThese agents are under clinical investigation and have not been proven to be safe and effective. There is no guarantee they will be approved in the sought-after indication. IFN, interferon; sc, subcutaneous; SmPC, Summary of Product Characteristics.

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Treatment Considerations for MS Must be Personalized to the Patient

- **Many factors impact treatment decisions in MS**

- Personal factors
 - Prognostic factors
 - Disease duration and level of disability
 - Risk aversion
- Burden of treatment
- Monitoring requirement
- De-risking strategies, e.g. JCV-testing

- **Ideally a therapy should**

- Be effective early in the disease course to maximize long-term outcomes
- Offer durability
- Have a well-characterized long-term safety profile
- Have a low treatment and management burden