


OhioHealth MS Center: *Hot Topics in MS*

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Disclosures

- Member of the speakers bureau for Novartis, Biogen, EMD Serono, Genentech, and Sanofi Genzyme
- Consultant for Bayer and Genentech





New and Emerging Multiple Sclerosis Disease Modifying Therapy

By Andrew Smith MD

OhioHealth MS Center: *Hot Topics in MS*

Overview

- New Disease Modifying Therapy (DMT)
  - Ocrelizumab
  - Ofatumumab
  - Cladribine
  - Sphingosine-1-Phosphate Receptor Modulators (S1P)
  - Fumarates
- Emerging Therapy
  - Bruton's Tyrosine Kinase Inhibitor (BTKi)

Overview of the review

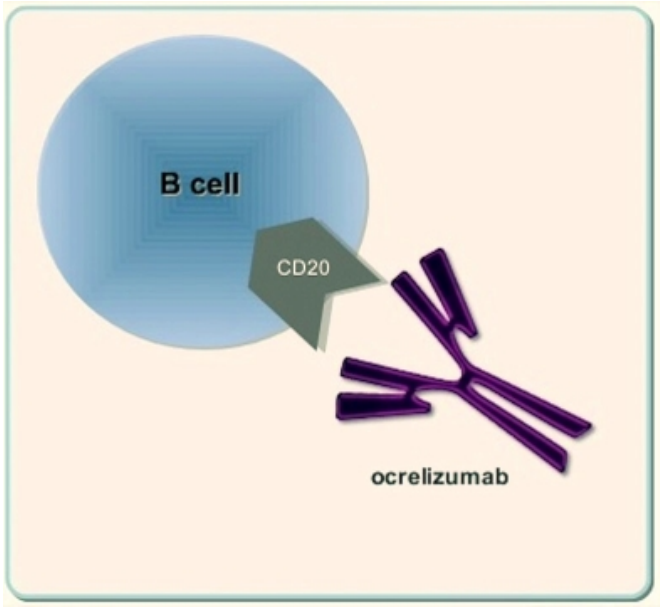
- Mechanism of Action (MOA)
- Pharmacodynamics (PD)
- Therapeutic monitoring recommendations (TMR)
- Black Box Warning (BBW)
- Efficacy (EF)
- Side Effect (SE)
- Active Research (AR)





Ocrelizumab (Ocrevus)

Ocrevus MOA



Monoclonal antibody (MAB) binds to CD20 that results in antibody-dependent cellular cytolysis and complement-mediated lysis.

Source: https://www.gene.com/download/pdf/ocrevus_prescribing.pdf

Ocrevus PD

Reduces CD19+ B-cell counts by 14 days after infusion.

Median time for B-cell counts to return to either baseline or LLN was 72 weeks (range 27-175 weeks) after the last OCREVUS infusion.

Source: https://www.gene.com/download/pdf/ocrevus_prescribing.pdf

Ocrevus TMR

- Baseline
  - CBC with diff, LFT's, Immunoglobins, Hepatitis, T-spot
    - Absolute Lymphocyte count (ABS LC) > or =Abs LC > or = 0.8
  - Vaccines 4-6 weeks prior to infusion

- Monitoring
  - Every 6 months CBC with diff, LFTs and immunoglobulins
  - MRI Brain (6 months after starting and then annually)

Ocrevus EF

Table 4 Key Clinical and MRI Endpoints in RMS Patients from Study 1 and Study 2

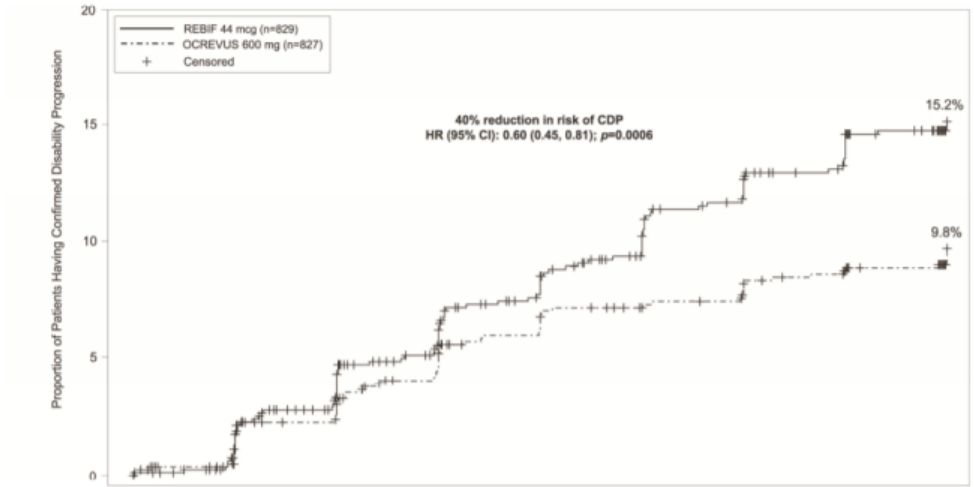
Endpoints	Study 1		Study 2	
	OCREVUS 600 mg every 24 weeks N=410	REBIF 44 mcg three times a week N=411	OCREVUS 600 mg every 24 weeks N=417	REBIF 44 mcg three times a week N=418
Clinical Endpoints				
Annualized Relapse Rate (Primary Endpoint)	0.156	0.292	0.155	0.290
Relative Reduction	46% (p<0.0001)		47% (p<0.0001)	
Proportion Relapse-free	83%	71%	82%	72%
Proportion of Patients with 12-week Confirmed Disability Progression[1]	9.8% OCREVUS vs 15.2% REBIF			
Risk Reduction (Pooled Analysis[2])	40%; p=0.0006			
MRI Endpoints				
Mean number of T1 Gd-enhancing lesions per MRI	0.016	0.286	0.021	0.416
Relative Reduction	94% (p<0.0001)		95% (p<0.0001)	
Mean number of new and/or enlarging T2 hyperintense lesions per MRI	0.323	1.413	0.325	1.904
Relative Reduction	77% (p<0.0001)		83% (p<0.0001)	

[1] Defined as an increase of 1.0 point or more from the baseline Expanded Disability Status Scale (EDSS) score for patients with baseline score of 5.5 or less, or 0.5 or more when the baseline score is greater than 5.5, Kaplan-Meier estimates at Week 96.
[2] Data prospectively pooled from Study 1 and Study 2.

Source: https://www.gene.com/download/pdf/ocrevus_prescribing.pdf

Ocrevus EF

Figure 1 Kaplan-Meier Plot* of Time to Onset of Confirmed Disability Progression Sustained for at Least 12 Weeks with the Initial Event of Neurological Worsening Occurring During the Double-blind Treatment Period in Pooled Studies 1 and 2 in Patients with RMS (Pooled ITT Population)



*Pre-specified pooled analysis of Study 1 and 2

Source: https://www.gene.com/download/pdf/ocrevus_prescribing.pdf

Ocrevus EF

Table 5 Key Clinical and MRI Endpoints in PPMS patients for Study 3

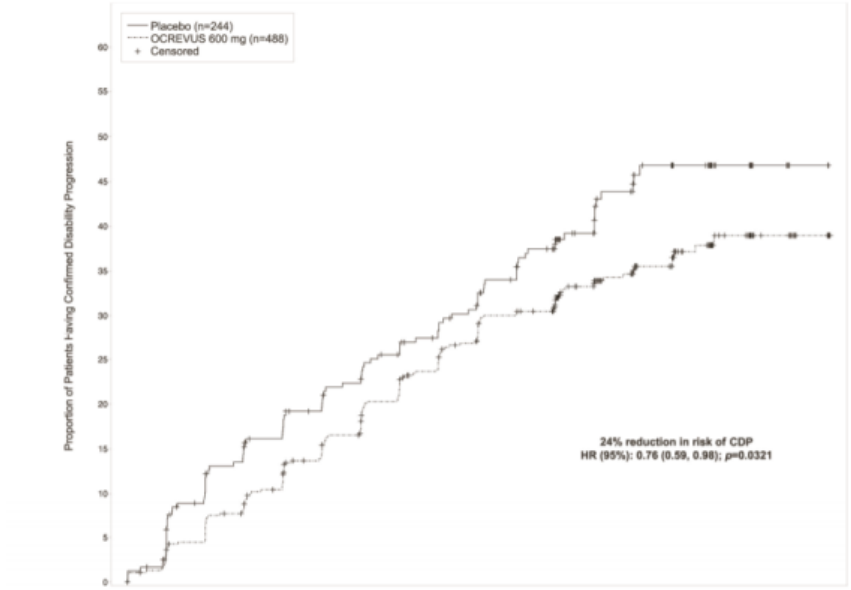
Endpoints	Study 3	
	OCREVUS 600 mg (two 300 mg infusions two weeks apart every 24 weeks) N=488	Placebo N=244
Clinical Outcomes		
Proportion of patients with 12-week Confirmed Disability Progression[1]	32.9%	39.3%
Risk reduction	24%; p=0.0321	
MRI Endpoints		
Mean change in volume of T2 lesions, from baseline to Week 120 (cm^3)	-0.39	0.79
	p<0.0001	

[1] Defined as an increase of 1.0 point or more from the baseline EDSS score for patients with baseline score of 5.5 or less, or an increase of 0.5 or more when the baseline score is more than 5.5

Source: https://www.gene.com/download/pdf/ocrevus_prescribing.pdf

Ocrevus EF

Figure 2 Kaplan-Meier Plot of Time to Onset of Confirmed Disability Progression Sustained for at Least 12 Weeks with the Initial Event of Neurological Worsening Occurring During the Double-blind Treatment Period in Study 3*



No. of Patients at Risk

	Baseline	12	24	36	48	60	72	84	96	108	120	132	144	156	168	180	192	204	216
Placebo	244	232	212	199	189	180	172	162	153	145	136	120	85	66	46	30	20	7	2
OCREVUS 600 mg	487	462	450	431	414	391	376	355	338	319	304	281	207	166	136	80	47	20	7

Source: https://www.gene.com/download/pdf/ocrevus_prescribing.pdf

Ocrevus SE

	OCREVUS 600 mg IV Every 24 Weeks[1] (n=825) %	REBIF 44 mcg SQ 3 Times per Week (n=826) %
Upper respiratory tract infections	40	33
Infusion reactions	34	10
Depression	8	7
Lower respiratory tract infections	8	5
Back pain	6	5
Herpes virus- associated infections	6	4
Pain in extremity	5	4

[1] The first dose was given as two separate 300 mg infusions at Weeks 0 and 2.

Source: https://www.gene.com/download/pdf/ocrevus_prescribing.pdf

Ocrevus SE

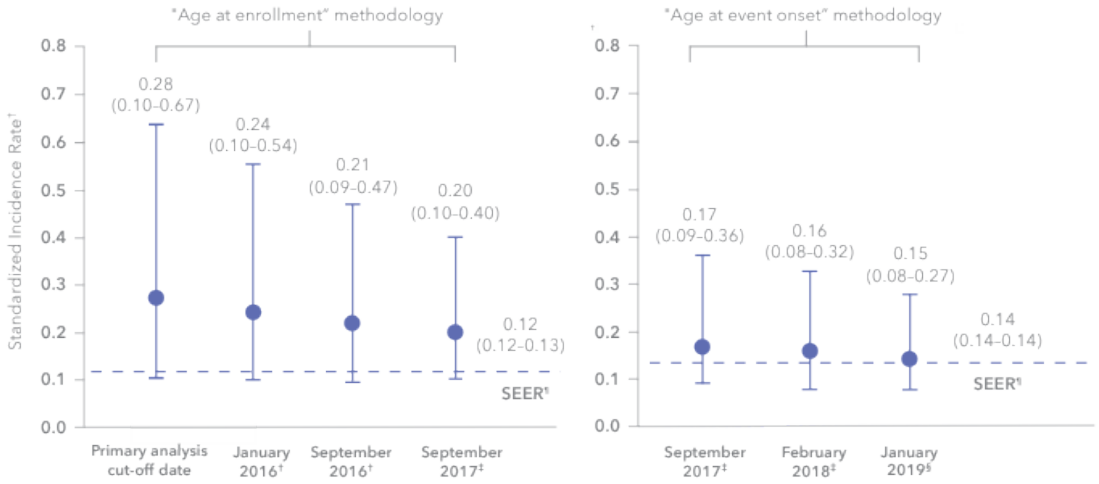
Table 3 Adverse Reactions in Adult Patients with PPMS with an Incidence of at least 5% for OCREVUS and Higher than Placebo

Adverse Reactions	Study 3	
	OCREVUS 600 mg IV Every 24 Weeks[1] (n=486) %	Placebo (n=239) %
Upper respiratory tract infections	49	43
Infusion reactions	40	26
Skin infections	14	11
Lower respiratory tract infections	10	9
Cough	7	3
Diarrhea	6	5
Edema peripheral	6	5
Herpes virus associated infections	5	4

[1] One dose of OCREVUS (600 mg administered as two 300 mg infusions two weeks apart)

Source: https://www.gene.com/download/pdf/ocrevus_prescribing.pdf

Ocrevus SE



Breast cancer was found in[1]:

6 OF 781 FEMALES ON OCREVUS VS **0** OF 668 FEMALES ON REBIF OR PLACEBO

in the OPERA and ORATORIO clinical trials

Breast cancer was found in[3]:

16 OF **2939 females on OCREVUS (8446 PY)**

in the all-exposure population of the clinical trials (data as of January 2019)

Source: https://www.ocrevus.com/hcp/rms/safety.html

Ocrevus SE

- **Infusion Reactions:** Management recommendations for infusion reactions depend on the type and severity of the reaction. Permanently discontinue OCREVUS if a life-threatening or disabling infusion reaction occurs
- **Infections:** Delay OCREVUS administration in patients with an active infection until the infection is resolved. Vaccination with live-attenuated or live vaccines is not recommended during treatment with OCREVUS and after discontinuation, until B-cell repletion
- **Reduction in Immunoglobulins:** Consider discontinuing OCREVUS in patients with serious opportunistic or recurrent serious infections, and if prolonged hypogammaglobulinemia requires treatment with intravenous immunoglobulins
- **Malignancies:** An increased risk of malignancy, including breast cancer, may exist with OCREVUS

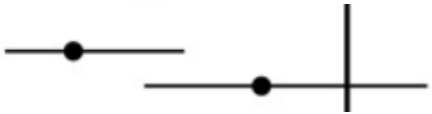
Source: https://www.gene.com/download/pdf/ocrevus_prescribing.pdf

Ocrevus AR

Ongoing trial: A Study to Evaluate the Efficacy, Safety and Pharmacokinetics of a Higher Dose of Ocrelizumab in Adults With Primary Progressive Multiple Sclerosis (PPMS)

- This is a randomized, double blind, controlled, parallel group, multicenter study to evaluate efficacy, safety and pharmacokinetics of a higher dose of ocrelizumab per intravenous (IV) infusion every 24 weeks in participants with PPMS, in comparison to the approved 600 mg dose of ocrelizumab

Baseline body mass index, kg/m²[a]				
<25	413	54	406	23
≥25	409	59	412	51



0.39 (95% CI: 0.24–0.64; p<0.001)

0.81 (95% CI: 0.55–1.18; p=0.3)

Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6469695/





Ofatumumab (Kesimpta)

Kesimpta MOA

- Selectively binding to sites on both the small and large extracellular loops of CD20.
- Then causes a delayed B-cell lysis by mechanisms such as complement-dependent cytotoxicity (CDC) and antibody-dependent cellular cytotoxicity (ADCC).

Source: https://www.novartis.us/sites/www.novartis.us/files/kesimpta.pdf

Kesimpta PD

- Reduction in B-cells to below the LLN
  - In 77.0% and 78.8% of patients in one week after treatment initiation,
  - In 95.0% and 95.8% of patients, respectively, two weeks after treatment initiation
- B-cell recoveries over the LLN in at least 50% of patients in 24 to 36 weeks post treatment discontinuation.

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Source: https://www.novartis.us/sites/www.novartis.us/files/kesimpta.pdf

Kesimpta Dosing

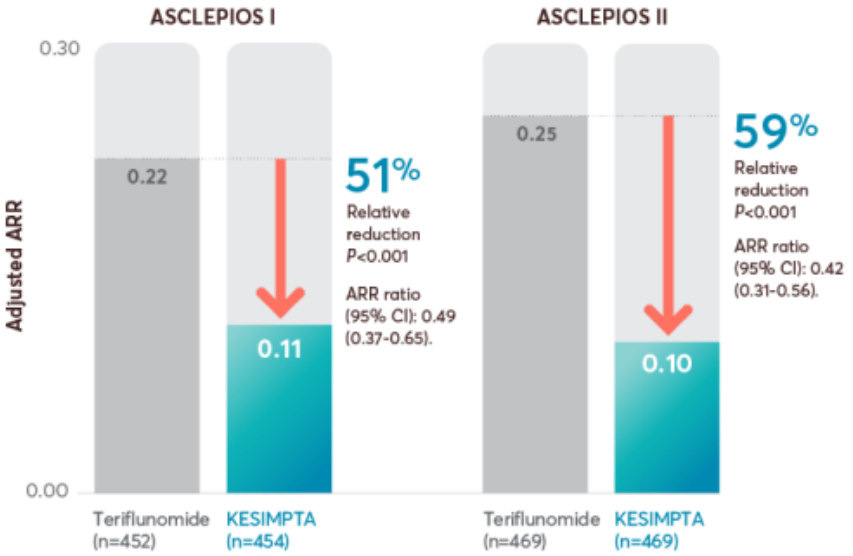
Source: https://www.novartis.us/sites/www.novartis.us/files/kesimpta.pdf

Kesimpta TMR

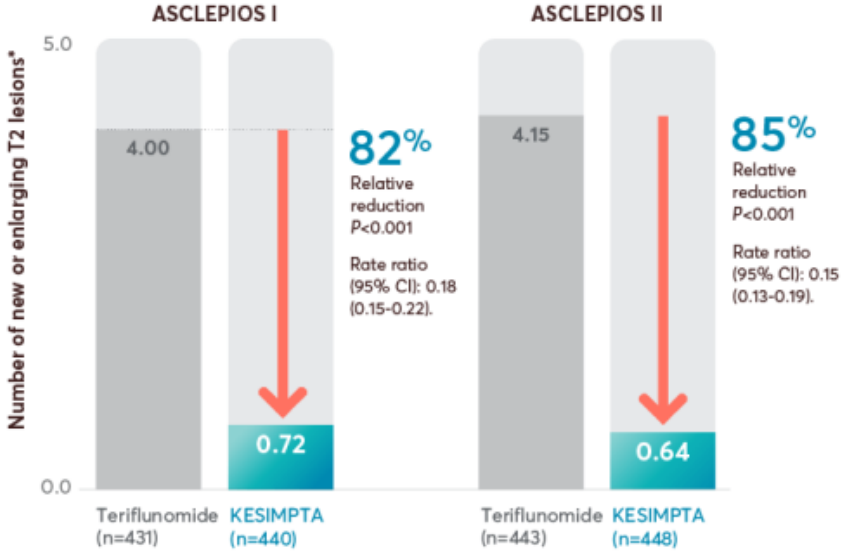
- Baseline
  - CBC with diff, LFT's, Immunoglobins, Hepatitis, T-spot
    - Absolute Lymphocyte count (ABS LC) > or =Abs LC > or = 0.8
  - Vaccines 4-6 weeks prior to infusion

- Monitoring
  - Every 6 months CBC with diff, LFTs and immunoglobulins
  - MRI Brain (6 months after starting and then annually)

Kesimpta EF



0.1 relapses per year is the equivalent of 1 relapse every 10 patient-years, based on ARR primary endpoint results[1,2]



Demonstrated near complete suppression of T2 lesion activity[1]

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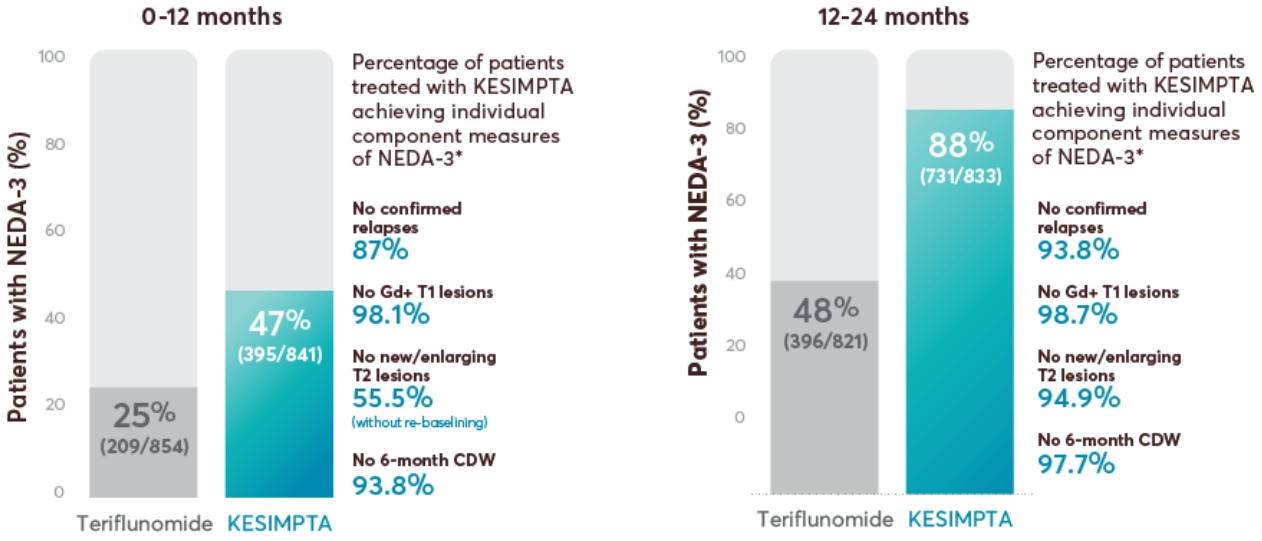
Source: https://www.hcp.novartis.com/products/kesimpta/rms/efficacy/

Kesimpta EF



Up to 9 out of 10 patients taking KESIMPTA achieved NEDA-3 in Year 2[3]

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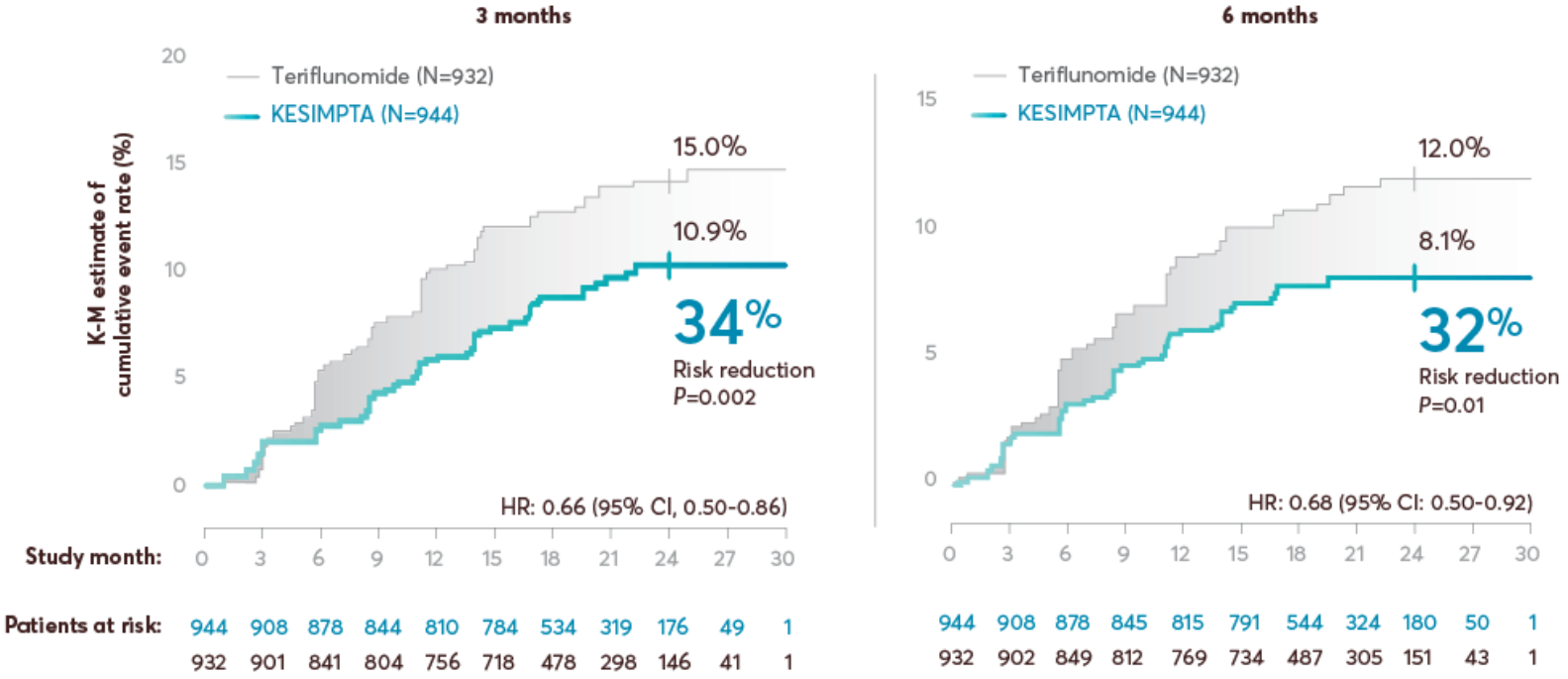
Source: https://www.hcp.novartis.com/products/kesimpta/rms/efficacy/

Kesimpta EF



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Source: https://www.hcp.novartis.com/products/kesimpta/rms/efficacy/

Kesimpta AE

Table 1: Adverse Reactions in Patients with RMS with an Incidence of at Least 5% with KESIMPTA and a Greater Incidence Than Teriflunomide (Pooled Study 1 and Study 2)

Adverse Reactions	KESIMPTA 20 mg N = 946 %	Teriflunomide 14 mg N = 936 %
Upper respiratory tract infections[a]	39	38
Injection-related reactions (systemic)	21	15
Headache	13	12
Injection-site reactions (local)	11	6
Urinary tract infection	10	8
Back pain	8	6
Blood immunoglobulin M decreased	6	2

[a]Includes the following: nasopharyngitis, upper respiratory tract infection, influenza, sinusitis, pharyngitis, rhinitis, viral upper respiratory infection, tonsillitis, acute sinusitis, pharyngotonsillitis, laryngitis, pharyngitis streptococcal, viral rhinitis, sinusitis bacterial, tonsillitis bacterial, viral pharyngitis, viral tonsillitis, chronic sinusitis, nasal herpes, tracheitis.

Source: https://www.novartis.us/sites/www.novartis.us/files/kesimpta.pdf

Kesimpta AE

- **Infections**: Delay KESIMPTA administration in patients with an active infection until the infection is resolved. Vaccination with live-attenuated or live vaccines is not recommended during treatment with KESIMPTA and after discontinuation, until B-cell repletion.
- **Injection-Related Reactions**: Management for injection-related reactions depends on the type and severity of the reaction.
- **Reduction in Immunoglobulins**: Monitor the level of immunoglobulins at the beginning, during, and after discontinuation of treatment with KESIMPTA until B-cell repletion. Consider discontinuing KESIMPTA if a patient develops a serious opportunistic infection or recurrent infections if immunoglobulin levels indicate immune compromise.
- **Fetal Risk**: May cause fetal harm based on animal data. Advise females of reproductive potential of the potential risk to a fetus and to use an effective method of contraception during treatment and for 6 months after stopping KESIMPTA.

Source: https://www.novartis.us/sites/www.novartis.us/files/kesimpta.pdf

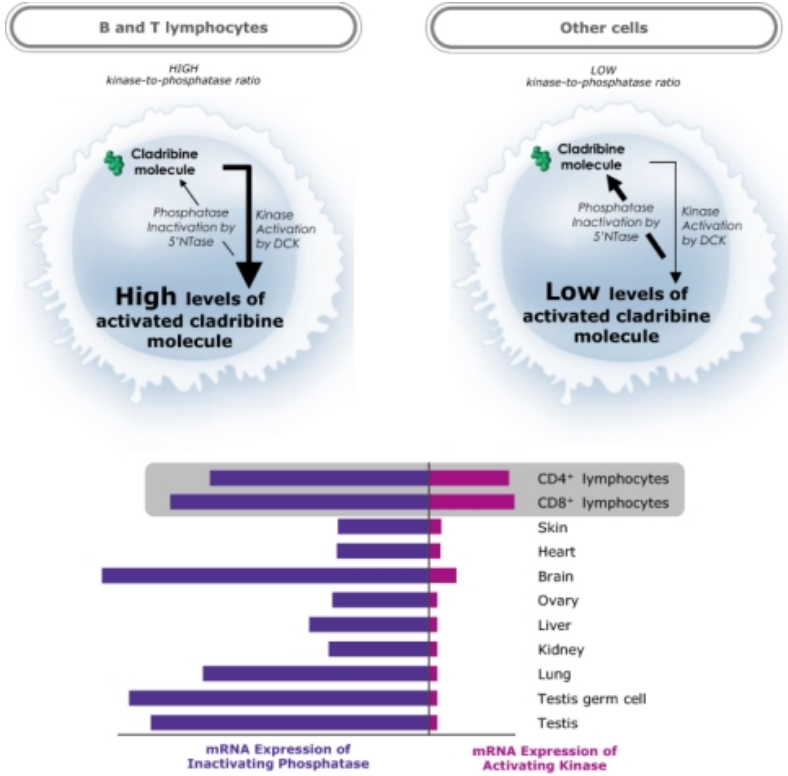




Cladribine (Mavenclad)

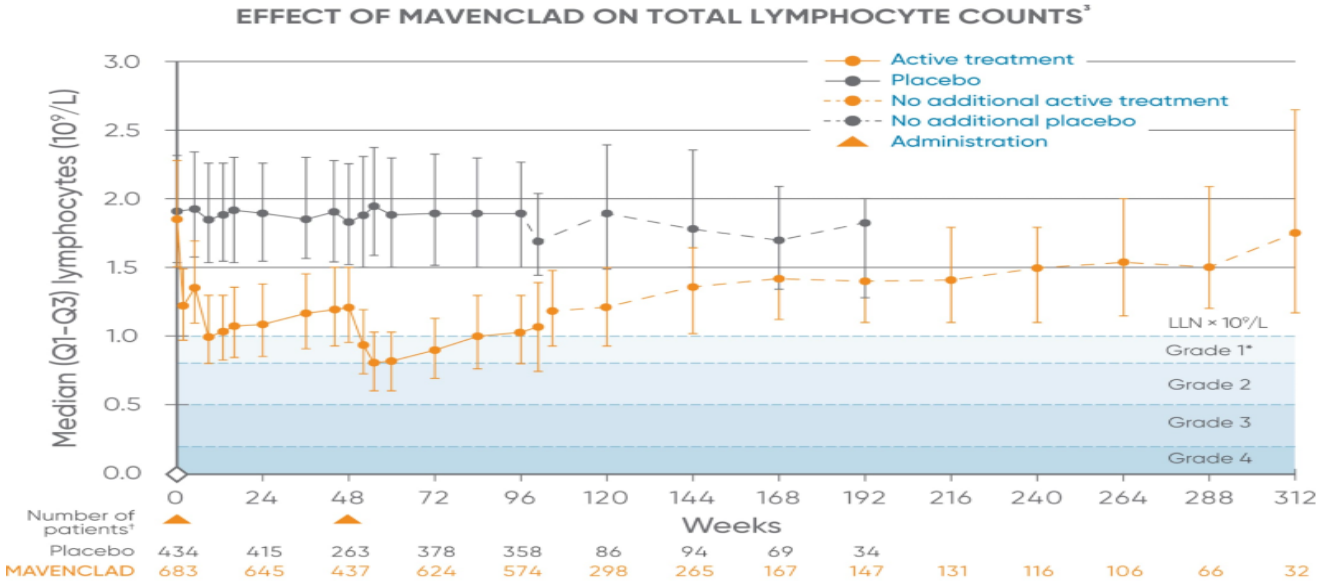
Mavenclad MOA

- Cytotoxic effects on B and T lymphocytes through impairment of DNA synthesis, resulting in depletion of lymphocytes
  - Cladribine enters cell via nucleoside transporter
  - Accumulates intracellularly due to ADA resistance
  - Cladribine is activated by specific kinases
  - Activated Cladribine induces selective lymphocyte reduction



Source: https://link.springer.com/article/10.1007/s40265-020-01422-9

Mavenclad PD



*Graded according to the Common Terminology Criteria for Adverse Events (version 5.0). 1, <LLN–800/µL; 2, <800–500/µL; 3, <500–200/µL; 4, <200/µL.[7]

†Visits with sample size ≥30 are displayed.

LLN: lower limit of normal.

Source: https://www.mavenclad.com/en/hcp/clinical-overview/efficacy.html

Mavenclad Dosing

Weight Range	Dose in mg (number of 10mg tablets) per treatment week	
kg	Treatment week 1	Treatment week 2
40 to <50	40mg (4 tablets)	40mg (4 tablets)
50 to <60	50mg (5 tablets)	50mg (5 tablets)
60 to <70	60mg (6 tablets)	60mg (6 tablets)
70 to <80	70mg (7 tablets)	70mg (7 tablets)
80 to <90	80mg (8 tablets)	70mg (7 tablets)
90 to <100	90mg (9 tablets)	80mg (8 tablets)
100 to <110	100mg (10 tablets)	90mg (9 tablets)

Source: https://www.mavenclad.com/en/hcp/clinical-overview/efficacy.html

Mavenclad TMR

- Initiation:
  - CBC with diff, LFT's, T-spot, hepatitis panel, VZV IgG, HIV
  - Vaccinate against varicella if not immune prior to starting
  - Age Appropriate Cancer Screening:
    - Women: Mammogram (age 40 unless high risk), Pap, Colonscopy (age 50 and up), Screening skin exam
    - Men: Colonoscopy, Screening skin exam

- Monitoring:
  - 2 months CBC with diff, & LFT's, 6 months and periodically thereafter

Mavenclad BBW

WARNING: MALIGNANCIES and RISK OF TERATOGENICITY

See full prescribing information for complete boxed warning.

- **Malignancies**

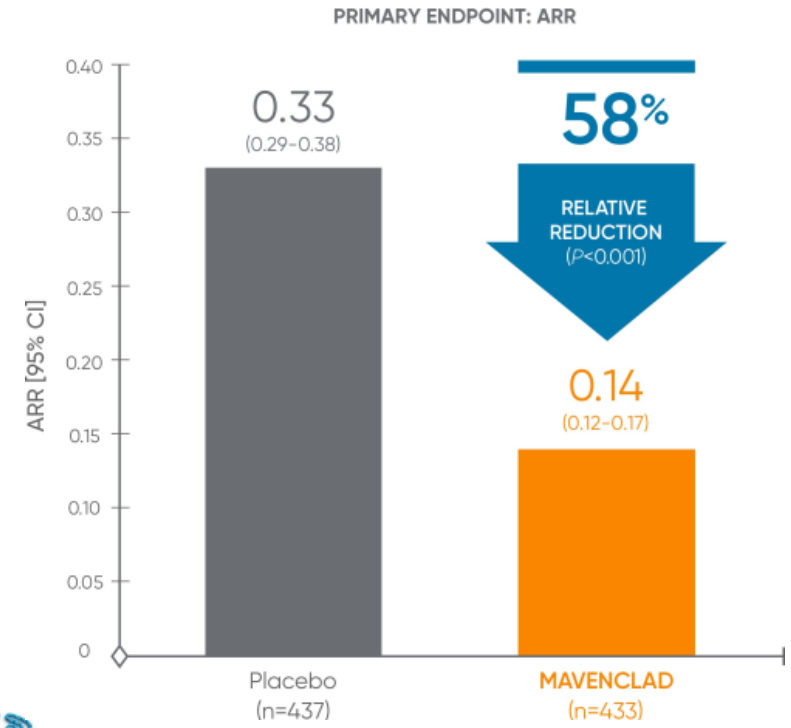
MAVENCLAD may increase the risk of malignancy. MAVENCLAD is contraindicated in patients with current malignancy; evaluate the benefits and risks on an individual basis for patients with prior or increased risk of malignancy. (5.1)

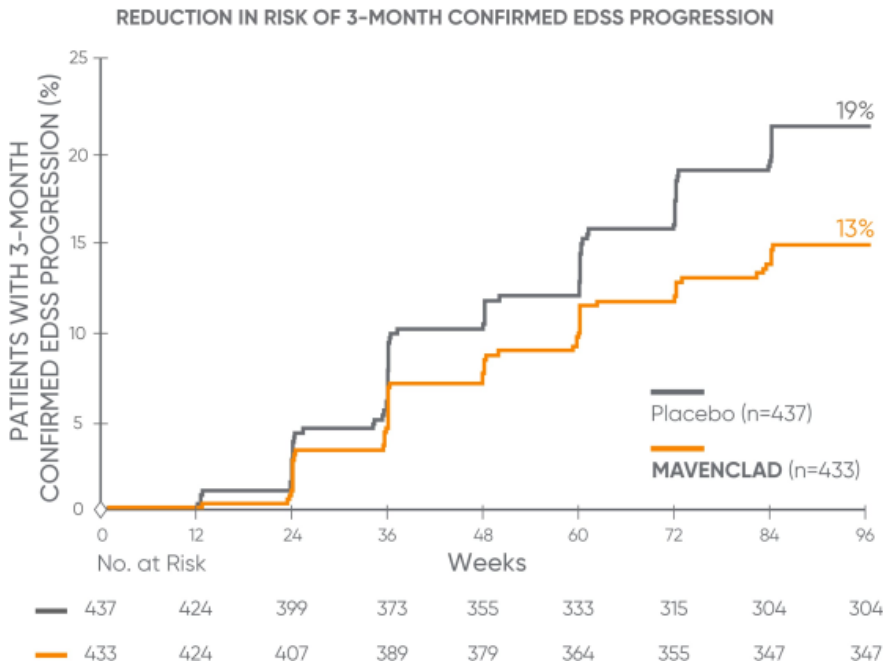
- **Risk of Teratogenicity**

MAVENCLAD is contraindicated for use in pregnant women and in women and men of reproductive potential who do not plan to use effective contraception because of the risk of fetal harm. (5.2)

Source: https://www.mavenclad.com/en/hcp/clinical-overview/efficacy.html

Mavenclad EF





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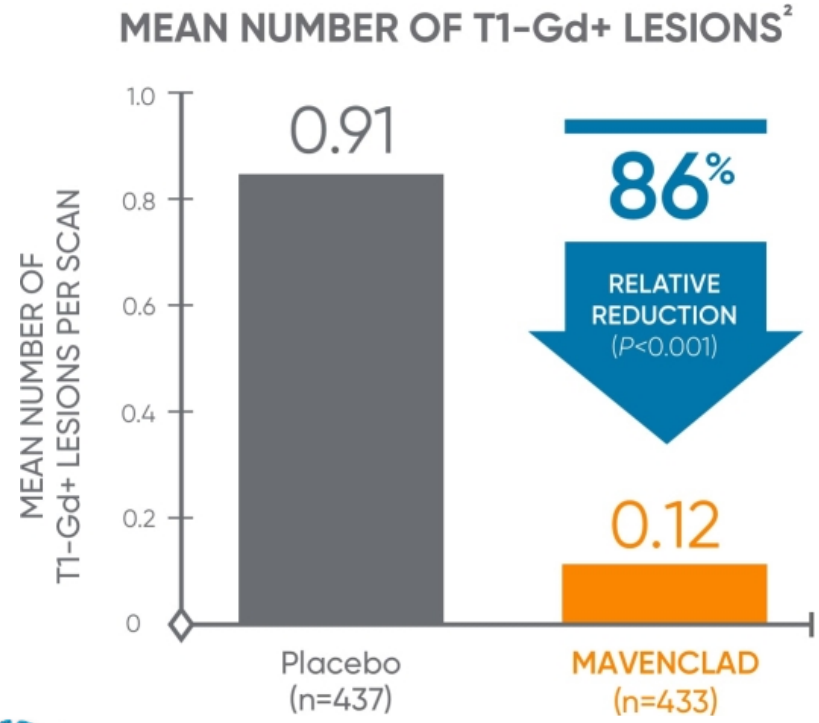
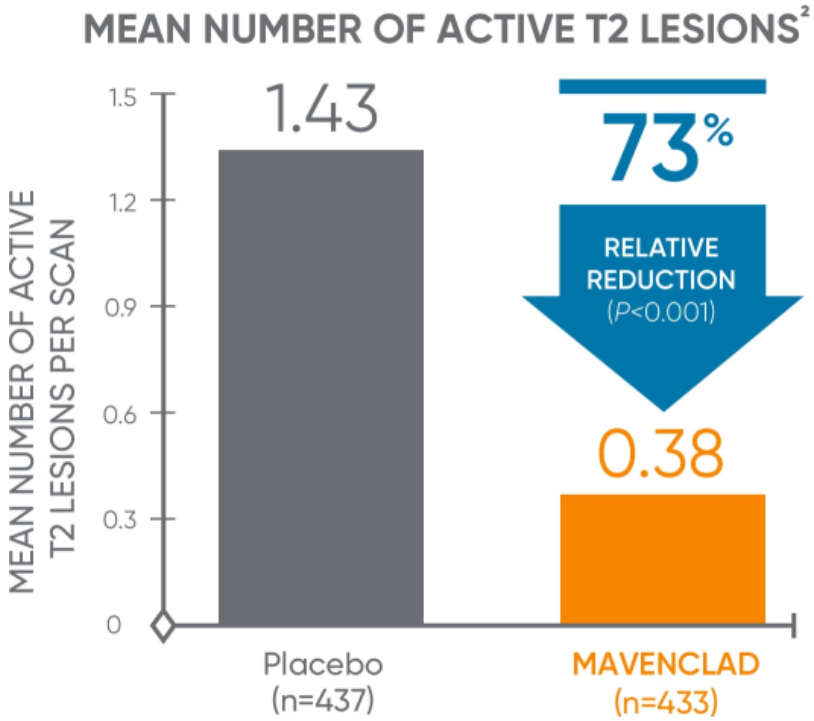
Source: https://www.mavenclad.com/en/hcp/clinical-overview/efficacy.html

Mavenclad EF





Source: https://www.mavenclad.com/en/hcp/clinical-overview/efficacy.html

Mavenclad EF

(OR: 4.28; 95% CI: 3.05–6.02, *P*<0.0001)

NEDA POST HOC ANALYSIS: OVERALL POPULATION[4]

RELAPSE FREE: **80%** MAVENCLAD (n=327/409) vs **60%** placebo (n=240/401)

3-MONTH EDSS PROGRESSION FREE*: **86%** MAVENCLAD (n=349/407) vs **79%** placebo (n=306/388)

T1-Gd+ LESION FREE: **87%** MAVENCLAD (n=368/422) vs **47%** placebo (n=201/424)

ACTIVE T2 LESION FREE: **62%** MAVENCLAD (n=261/422) vs **28%** placebo (n=117/424)

Source: https://www.mavenclad.com/en/hcp/clinical-overview/efficacy.html

Mavenclad AE

Table 2 **Adverse Reactions in Study 1 with an Incidence of at Least 5% for MAVENCLAD and Higher than Placebo**

	MAVENCLAD (N=440) %	Placebo (N=435) %
Upper respiratory tract infection	38	32
Headache	25	19
Lymphopenia	24	2
Nausea	10	9
Back pain	8	6
Arthralgia and arthritis	7	5
Insomnia	6	4
Bronchitis	5	3
Hypertension	5	3
Fever	5	3
Depression	5	3

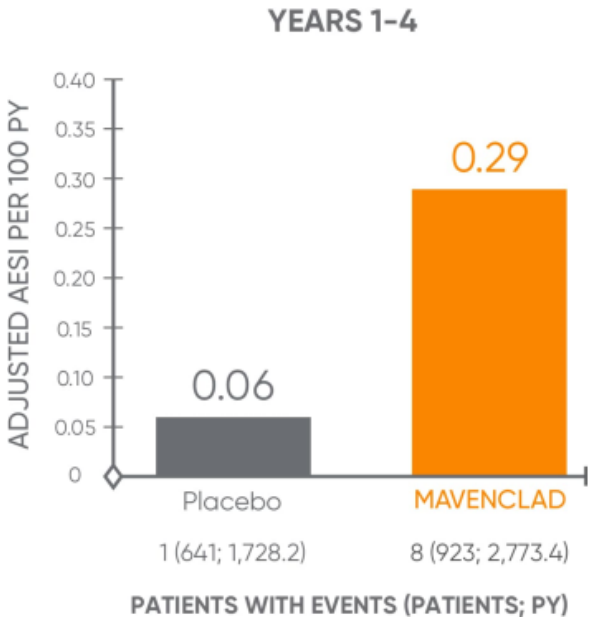
Source: https://www.mavenclad.com/content/dam/web/healthcare/neurology/united-states/pdfs/Prescribing%20Information.pdf

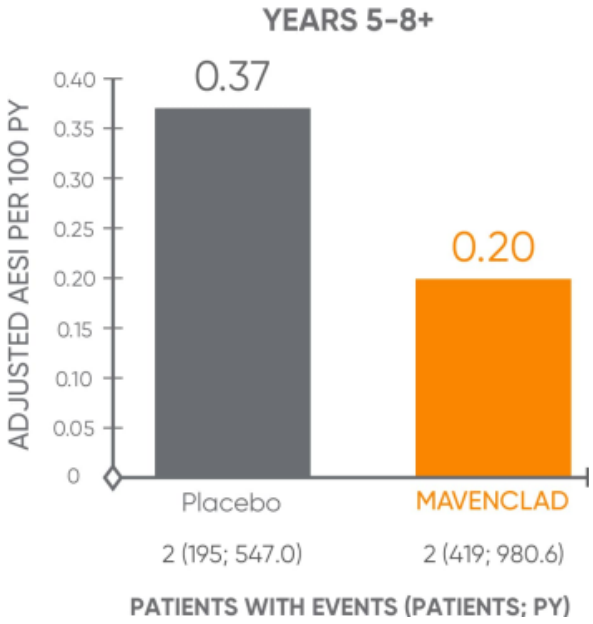
Mavenclad AE

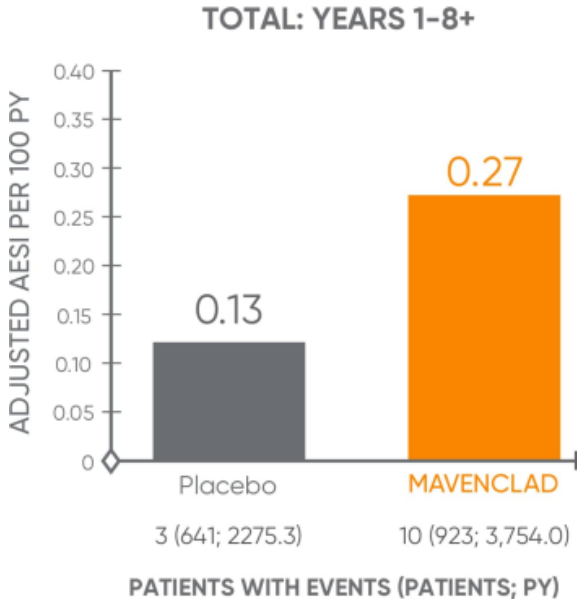
- **Lymphopenia:** Monitor lymphocyte counts before, during and after treatment.
- **Infections:** Screen patients for latent infections; consider delaying treatment until infection is fully controlled. Vaccinate patients antibody negative to varicella zoster virus prior to treatment. Administer anti-herpes prophylaxis in patients with lymphocyte counts less than 200 cells per microliter. Monitor for infections.
- **Hematologic toxicity:** Monitor complete blood count before, during and after treatment.
- **Graft-versus-host-disease with blood transfusion:** Irradiation of cellular blood components is recommended.
- **Liver injury:** Obtain tests prior to treatment. Discontinue if clinically significant injury is suspected.

Source: https://www.mavenclad.com/content/dam/web/healthcare/neurology/united-states/pdfs/Prescribing%20Information.pdf

Mavenclad Cancer Risk







Source: https://www.mavenclad.com/content/dam/web/healthcare/neurology/united-states/pdfs/Prescribing%20Information.pdf





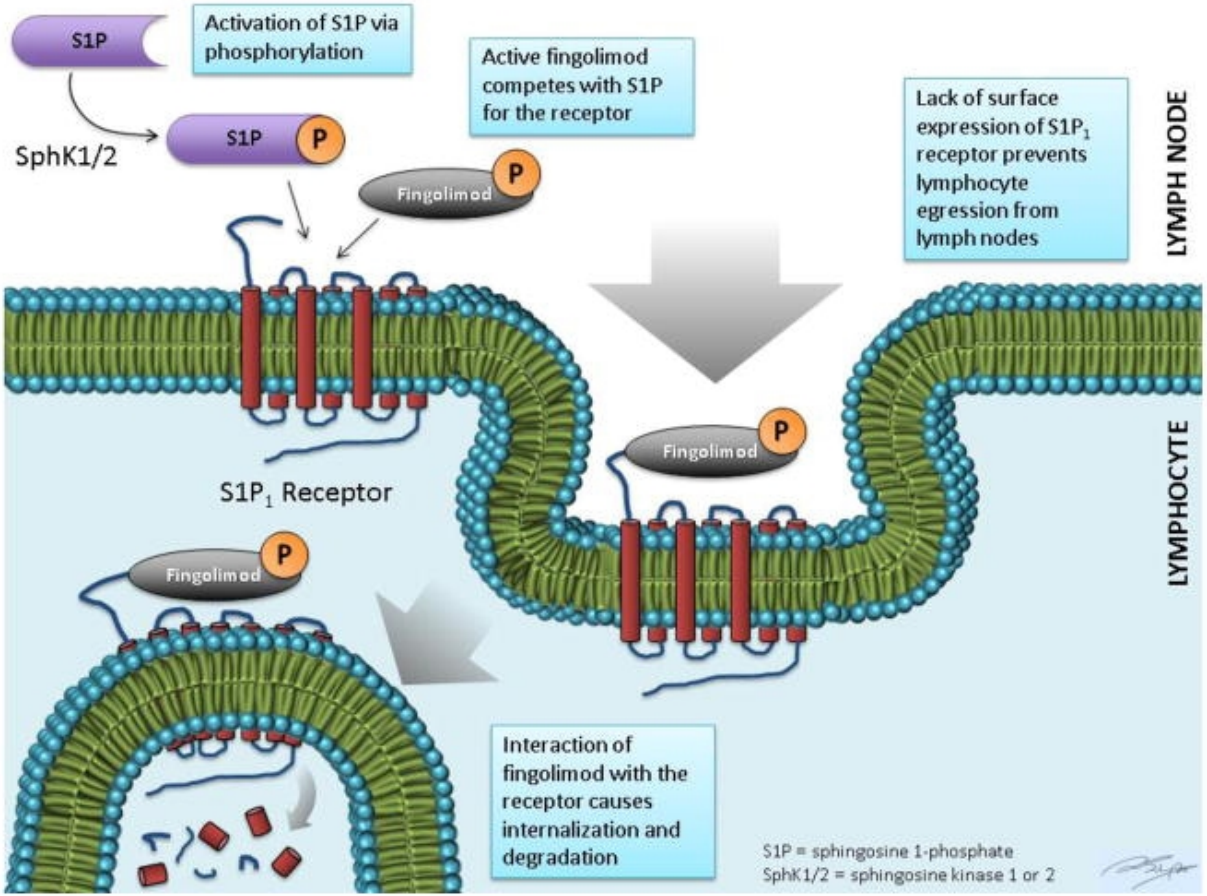
Sphingosine-1-Phosphate (S1P)

S1P Medications and Dosing

- Nonspecific S1P
  - Fingolimod 0.5mg (Gilenya)
- Selective S1P
  - Siponimod varies (Mayzent)
  - Ozanimod 0.92mg (Zeposia)
  - Ponesimod 20mg (Ponvory)

Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4554772/figure/F1/

S1P MOA



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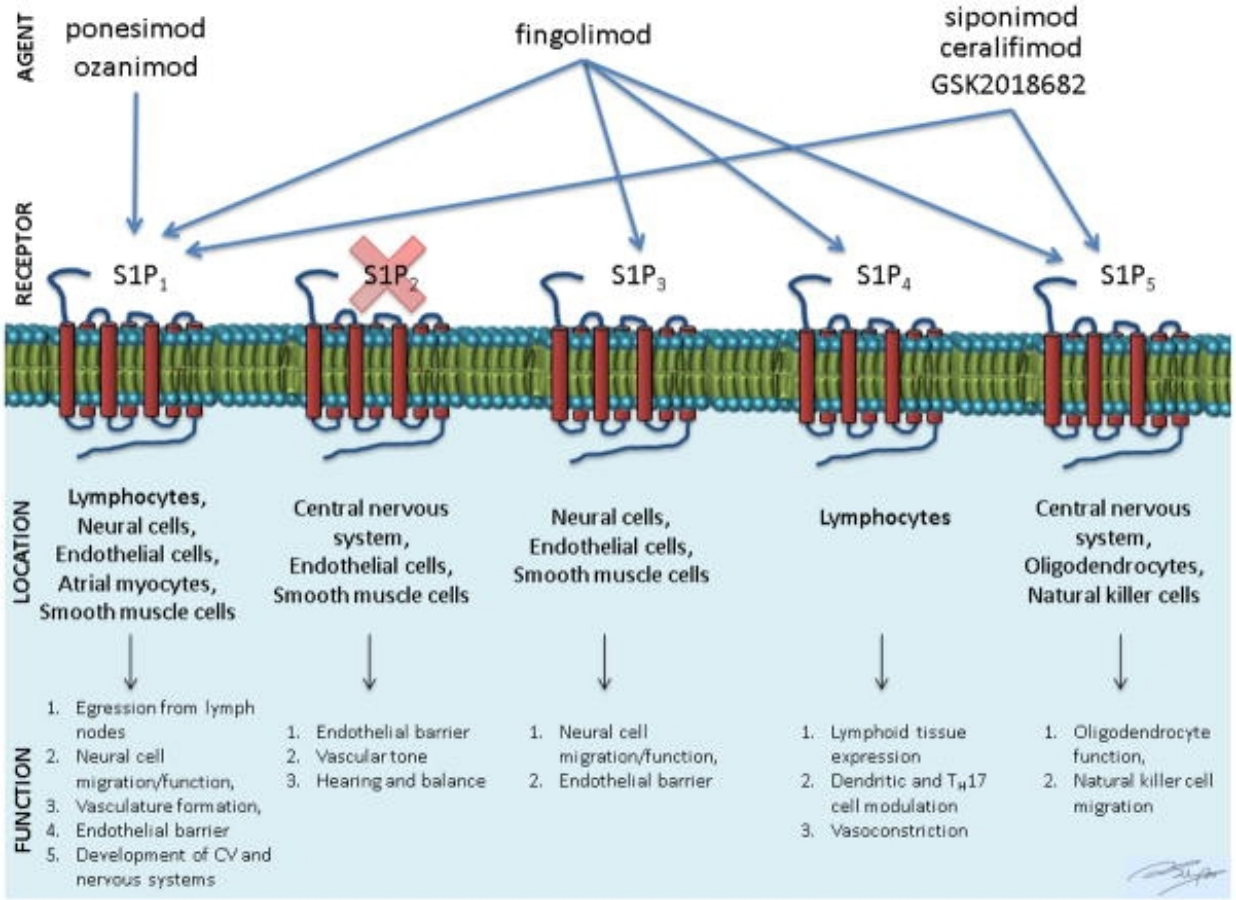
S1P MOA

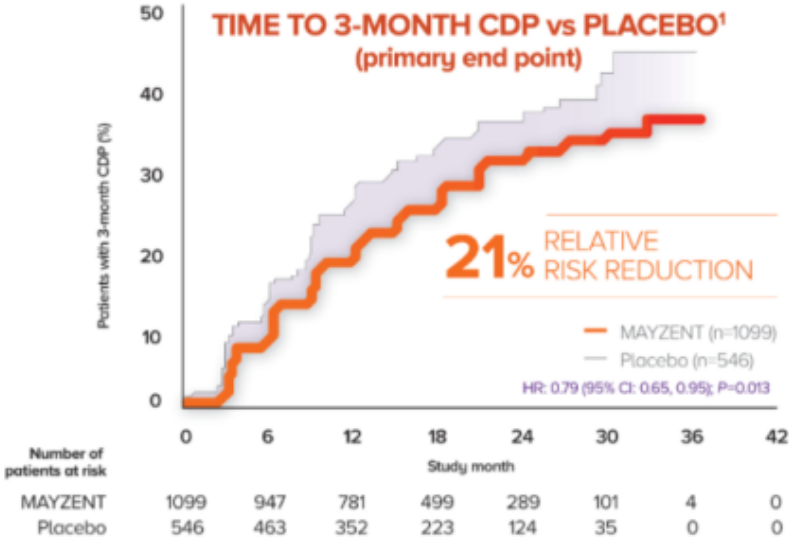


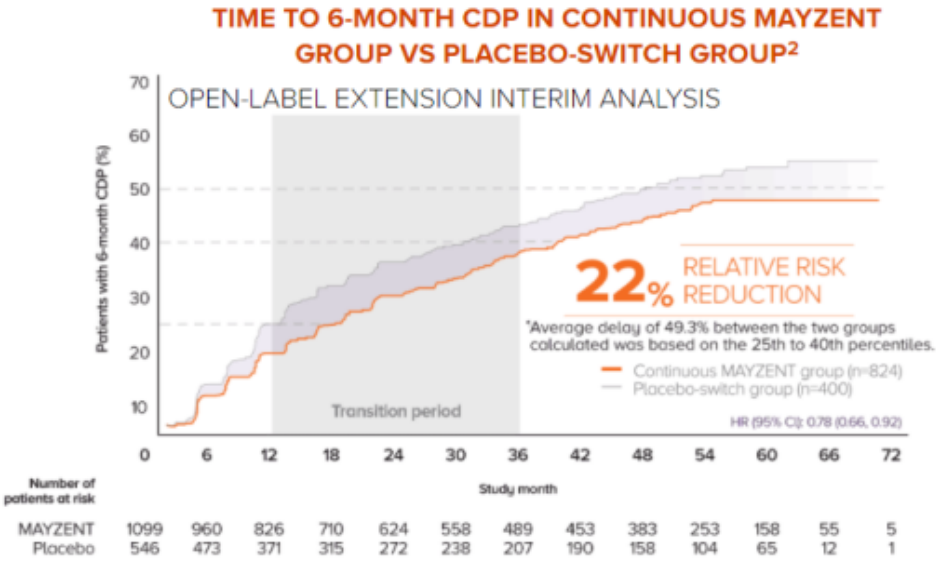
Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4554772/figure/F2/

S1P TMR

- Initiation:
  - CYP2C9*3/*3 genotype testing (siponimod only)
    - CYP2C9*3/*3 genotype do not use
    - CYP2C9*1/*3 or *2/*3 genotype dose 1 mg
    - Other genotype dose 2mg
  - EKG
  - Fundus photo/Macular exam by ophtho (not required for ozanimod)
  - CBC with diff, LFT's, VZV IgG
  - Vaccinate against varicella if not immune prior to initiation
- Monitoring:
  - CBC with diff and LFT's every 6 months
  - Fundus photo at 3-4 months, 6, 9, 12 months (fingolimod, siponimod)

Mayzent EF





Source: https://www.mayzenthcp.com/clinical-data/efficacy

Mayzent EF

Table 4 Clinical and MRI Results From Study 1

	MAYZENT	PLACEBO
Clinical Outcomes		
Proportion of patients with confirmed disability progression[1]	26%	32%
Relative risk reduction	21% ($p = 0.0134$)*	
Absolute risk Reduction	6%	
Proportion of patients with confirmed worsening in timed 25-foot walk	40%	41%
	p = NS	
Annualized relapse rate[2]	0.071	0.160
Relative reduction (%)	55% ($p < 0.01$)^	
Absolute reduction	0.089	
	$p < 0.01$^	
MRI Endpoints		
Change from baseline in T2 lesion volume (mm^3) (95% CI)[3]	184 (54; 314)	879 (712; 1047)
	$p < 0.01$^	

Source: https://www.mayzenthcp.com/clinical-data/efficacy

Mayzent AE

- **Infections:** Obtain a CBC before initiating treatment. Monitor for infection during treatment. Do not start in patients with active infection.
- **Macular Edema:** An ophthalmic evaluation is recommended before starting treatment and if there is any change in vision while taking MAYZENT. Diabetes mellitus and uveitis increase the risk.
- **Bradyarrhythmia and Atrioventricular Conduction Delays:** MAYZENT may result in a transient decrease in heart rate; titration is required for treatment initiation. Consider resting heart rate with concomitant beta blocker use; obtain cardiologist consultation before concomitant use with other drugs that decrease heart rate.
- **Respiratory Effects:** May cause a decline in pulmonary function. Assess pulmonary function (e.g., spirometry) if clinically indicated.
- **Liver Injury:** Obtain liver enzyme results before initiation. Closely monitor patients with severe hepatic impairment. Discontinue if significant liver injury occurs.
- **Cutaneous Malignancies:** Periodic skin examination is recommended.
- **Increased Blood Pressure:** Monitor blood pressure (BP) during treatment.
- **Fetal Risk:** Women of childbearing potential should use effective contraception during and for 10 days after stopping MAYZENT

Source: https://www.mayzenthcp.com/clinical-data/efficacy

Mayzent AE

Table 3 Adverse Reactions Reported in Study 1 (Occurring in at Least 5% of MAYZENT-Treated Patients and at a Rate at Least 1% Higher Than in Patients Receiving Placebo)

Adverse Reaction	MAYZENT 2 mg (N = 1099) %	Placebo (N = 546) %
Headache[a]	15	14
Hypertension[b]	13	9
Transaminase increased[c]	11	3
Falls	11	10
Edema peripheral[d]	8	4
Nausea	7	4
Dizziness	7	5
Diarrhea	6	4
Bradycardia[e]	6	3
Pain in extremity[f]	6	4

Terms were combined as follows:

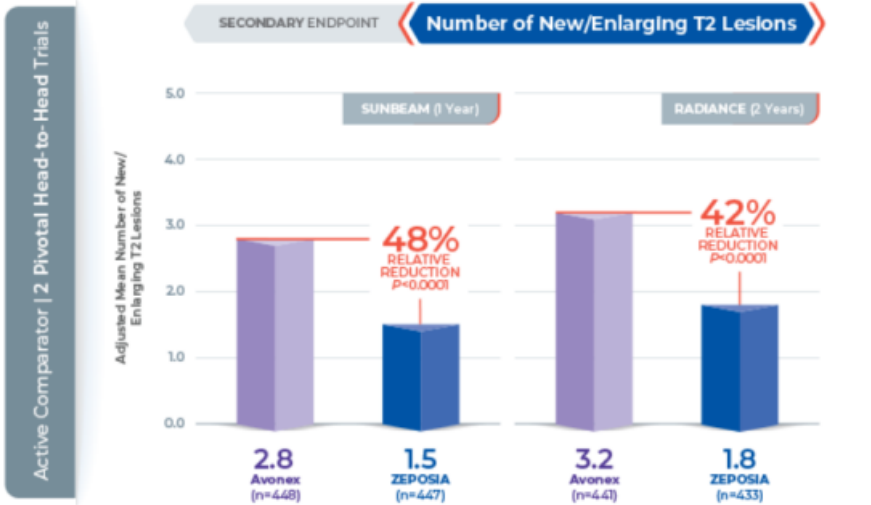
[a]headache, tension headache, sinus headache, cervicogenic headache, drug withdrawal headache, and procedural headache.
[b]hypertension, blood pressure increased, blood pressure systolic increased, essential hypertension, blood pressure diastolic increased.
[c]alanine aminotransferase increased, gamma-glutamyltransferase increased, hepatic enzyme increased, aspartate aminotransferase increased, blood alkaline phosphatase increased, liver function test increased, hepatic function abnormal, liver function test abnormal, transaminases increased.
[d]edema peripheral, joint swelling, fluid retention, swelling face.
[e]bradycardia, sinus bradycardia, heart rate decreased.
[f]pain in extremity and limb discomfort.

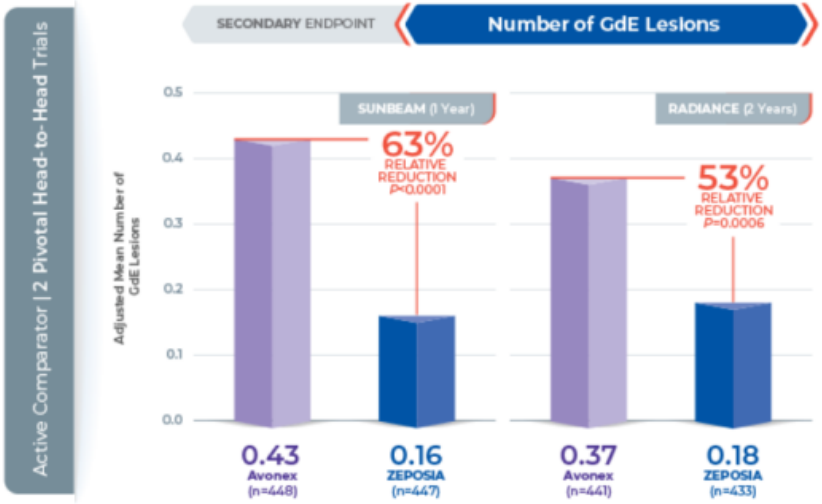
Source: https://www.mayzenthcp.com/clinical-data/efficacy

Zeposia EF

Source: https://www.zeposiahcp.com/efficacy-and-study-results/

Zeposia EF





Source: https://www.zeposiahcp.com/efficacy-and-study-results/

Zeposia SE

- **Infections:** ZEPOSIA may increase the risk of infections. Obtain a CBC before initiation of treatment. Monitor for infection during treatment and for 3 months after discontinuation. Do not start ZEPOSIA in patients with active infections.
- **Bradyarrhythmia and Atrioventricular Conduction Delays:** ZEPOSIA (ozanimod) may result in transient decrease in heart rate; titration is required for treatment initiation. Check an ECG to assess for preexisting cardiac conduction abnormalities before starting ZEPOSIA. Consider cardiology consultation for conduction abnormalities or concomitant use with other drugs that decrease heart rate.
- **Liver Injury:** Discontinue if significant liver injury is confirmed. Obtain liver function tests before initiating.
- **Fetal Risk:** Women of childbearing potential should use effective contraception during treatment and for 3 months after stopping ZEPOSIA .
- **Increased Blood Pressure (BP):** Monitor BP during treatment
- **Respiratory Effects:** May cause a decline in pulmonary function. Assess pulmonary function (e.g., spirometry) if clinically indicated.
- **Macular Edema:** A prompt ophthalmic evaluation is recommended if there is any change in vision while taking ZEPOSIA. Diabetes mellitus and uveitis increase the risk of macular edema; patients with a history of these conditions should have an ophthalmology evaluation before starting treatment.

Source: https://www.zeposiahcp.com/efficacy-and-study-results/

Zeposia SE

Table 2: Adverse Reactions with an Incidence of at Least 2% in ZEPOSIA-Treated Patients and at Least 1% Greater than IFN beta-1a[a] (Pooled Study 1 and Study 2)

Adverse Reactions	Studies 1 and 2	
	ZEPOSIA 0.92 mg (n=882) %	IFN beta-1a 30 mcg Intramuscularly Once Weekly (n=885) %
Upper respiratory infection[b]	26	23
Hepatic transaminase elevation[c]	10	5
Orthostatic hypotension	4	3
Urinary tract infection	4	3
Back pain	4	3
Hypertension[d]	4	2
Abdominal pain upper	2	1

Source: https://www.zeposiahcp.com/efficacy-and-study-results/

Ponvory Clinical Trial Data EF

- OPTIMUM (Phase 3 Trials)
- For ARR, the ponesimod group had a rate of 0.202 compared with 0.290 for the teriflunomide group (relative rate reduction, 30.5%; *P* = .0003)
- The respective ponesimod versus teriflunomide findings for the mean number of combined unique active lesions (CUALs) per year on MRI were 1.405 for the ponesimod group versus 3.164 for the teriflunomide group (relative rate reduction, 56%; *P* <.0001).
- Brain volume loss at week 108 for the ponesimod and teriflunomide groups respectively were −0.91% and −1.25% (reduced by 0.34 points; *P* <.0001), while NEDA-3 was achieved in 25.0% and 16.4% of patients, respectively (odds ratio [OR], 1.70; *P* = .0004).

Source: https://www.neurologylive.com/view/ponesimod-displays-superiority-in-relapsing-ms-treatment

Ponvory EF

Table 4: Clinical and MRI Endpoints from Study 1

Endpoints	**PONVORY 20 mg** N =567	**Teriflunomide 14 mg** N =566
Clinical Endpoints		
Annualized Relapse Rate[a]	0.202	0.290
Relative reduction	30.5% (p=0.0003)	
Percentage of patients without relapse[b]	70.7%	60.6%
Proportion of Patients with 3-month Confirmed Disability Progression[c]	10.8%	13.2%
Hazard Ratio[d]	0.83 (p=0.29)[e]	
MRI Endpoints[b, f]		
Mean number of new or enlarging T2 hyperintense lesions per year	1.40	3.16
Relative reduction	55.7% (p <.0001)	
Mean number of T1 Gd-enhancing lesions per MRI	0.18	0.43
Relative reduction	58.5% (p <.0001)	

Source: https://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/PONVORY-pi.pdf

Ponvory EF

Table 3: Adverse Reactions Reported in Study 1 Occurring in at Least 2% of PONVORY-Treated Patients and at a Higher Rate Than in Patients Receiving Teriflunomide 14 mg

Adverse Reaction	PONVORY N=565 (%)	Teriflunomide 14 mg N=566 (%)
Upper respiratory infection [a]	37	34
Hepatic transaminase elevation [b]	23	12
Hypertension [c]	10	9
Urinary tract infection	6	5
Dyspnea	5	1
Dizziness	5	3
Cough	4	2
Pain in extremity	4	3
Somnolence	3	2
Pyrexia	2	1
C-reactive protein increased	2	1
Hypercholesterolemia	2	1
Vertigo	2	1

[a] Includes the following terms: nasopharyngitis, upper respiratory tract infection, pharyngitis, respiratory tract infection

Source: https://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/PONVORY-pi.pdf





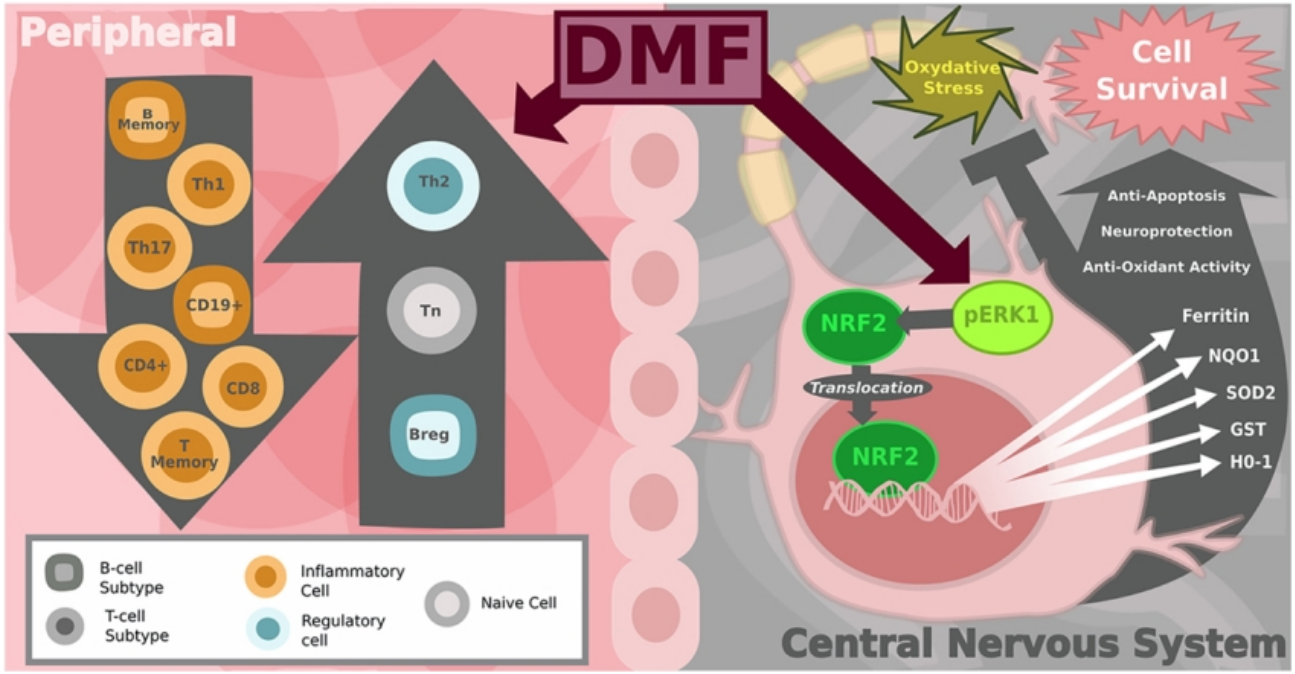
Fumarates

Fumarate Medications

- Dimethyl Fumarate 240mg (Tecfidera)
- Monomethyl Fumarate 190mg (Bafiertam)
- Diroximel Fumarate 462mg (Vumerity)

Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4554772/figure/F1/

Fumarate MOA



Fumarate TMR

- **Initiation:** CBC with diff, LFT's at baseline
- **Monitoring:** CBC with diff and LFT's every 3 months x 1 year, then every 6 months
- Take off if Absolute LC < 0.8
- **Transition off:** immediately ok to switch if Abs LC > 0.8, if not consider waiting until it is > or = 0.8

Fumarate EF

Table 2: Clinical and MRI Results of Study 1

	Dimethyl Fumarate 240 mg BID	Placebo	P-value
Clinical Endpoints	N=410	N=408	
Proportion relapsing (primary endpoint)	27%	46%	<0.0001
Relative risk reduction	49%		
Annualized relapse rate	0.172	0.364	<0.0001
Relative reduction	53%		
Proportion with disability progression	16%	27%	0.0050
Relative risk reduction	38%		
MRI Endpoints	N=152	N=165	
Mean number of new or newly enlarging T2 lesions over 2 years	2.6	17	<0.0001
Percentage of subjects with no new or newly enlarging lesions	45%	27%	
Number of Gd+ lesions at 2 years Mean (median)	0.1 (0)	1.8 (0)	
Percentage of subjects with			
0 lesions	93%	62%	
1 lesion	5%	10%	
2 lesions	<1%	8%	
3 to 4 lesions	0	9%	
5 or more lesions	<1%	11%	
Relative odds reduction (percentage)	90%		<0.0001
Mean number of new T1 hypointense lesions over 2 years	1.5	5.6	<0.0001

Source: https://www.vumerity.com/content/dam/commercial/vumerity/pat/en_us/pdf/vumerity-prescribing-information.pdf

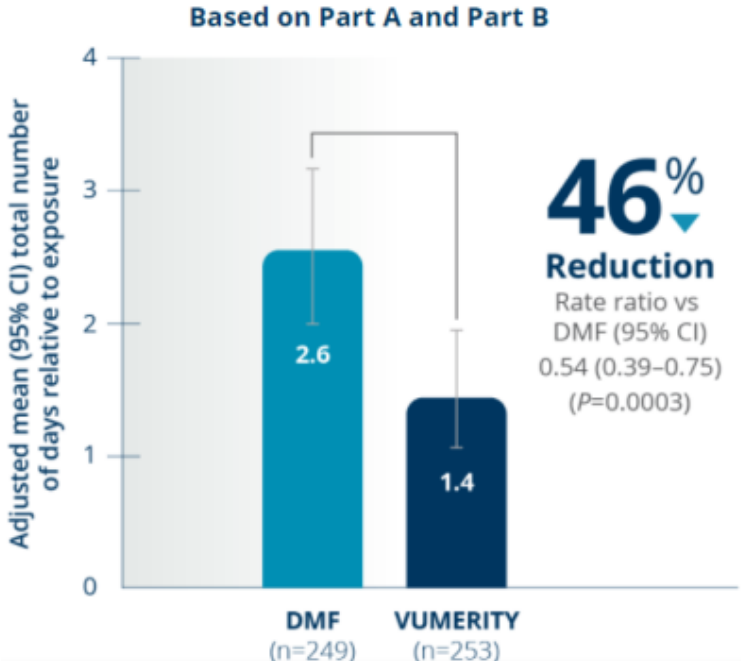
Fumarate SE

Table 1: Adverse Reactions in Study 1 and 2 Reported for Dimethyl Fumarate at ≥2% Higher Incidence than Placebo

Adverse Reactions	Dimethyl Fumarate 240 mg Twice Daily (N=769) %	Placebo (N=771) %
Flushing	40	6
Abdominal pain	18	10
Diarrhea	14	11
Nausea	12	9
Vomiting	9	5
Pruritus	8	4
Rash	8	3
Albumin urine present	6	4
Erythema	5	1
Dyspepsia	5	3
Aspartate aminotransferase increased	4	2
Lymphopenia	2	<1

Source: https://www.vumerity.com/content/dam/commercial/vumerity/pat/en_us/pdf/vumerity-prescribing-information.pdf

Fumarate SE



Source: https://www.vumerityhcp.com/en_us/home/safety/gi-tolerability-results.html?tabKey=tab_21

Fumarate SE

- **Anaphylaxis and Angioedema:** Discontinue and do not restart Fumarate if these occur.
- **Progressive Multifocal Leukoencephalopathy (PML):** Withhold Fumarate at the first sign or symptom suggestive of PML.
- Herpes zoster and other serious opportunistic infections
- **Lymphopenia:** Obtain a CBC including lymphocyte count

Source: https://www.vumerity.com/content/dam/commercial/vumerity/pat/en_us/pdf/vumerity-prescribing-information.pdf





Evolving Therapies

Bruton's tyrosine kinase inhibitors (BTK)

Table 1 | BTK inhibitors in clinical development for autoimmune disorders

Drug	Lead developer(s)	BTK binding mechanism	Lead indication(s)	Phase
Evobrutinib	Merck KGaA	Covalent, irreversible	MS	3
Tolebrutinib	Sanofi/Principia	Covalent, irreversible	MS	3
Fenebrutinib	Genentech	Non-covalent, reversible	MS	3
Rilzabrutinib	Sanofi/Principia	Covalent, reversible	Pemphigus vulgaris, immune thrombocytopenia	3
Remibrutinib	Novartis	Covalent, irreversible	Urticaria	2
Tirabrutinib	Gilead Sciences, Ono Pharmaceutical	Covalent, irreversible	Pemphigus vulgaris	2
Branebrutinib	Bristol Myers Squibb	Covalent, irreversible	Rheumatoid arthritis, lupus, Sjögren's syndrome	2
Orelabrutinib	InnoCare	Covalent, irreversible	MS	2
BIIB091	Biogen	Non-covalent, reversible	MS	1
AC0058	Acea Therapeutics	Covalent, irreversible	Lupus	1
PRN473	Sanofi/Principia	Covalent, reversible	Dermatology	1

Source: https://www.nature.com/articles/s41587-020-00790-7.pdf

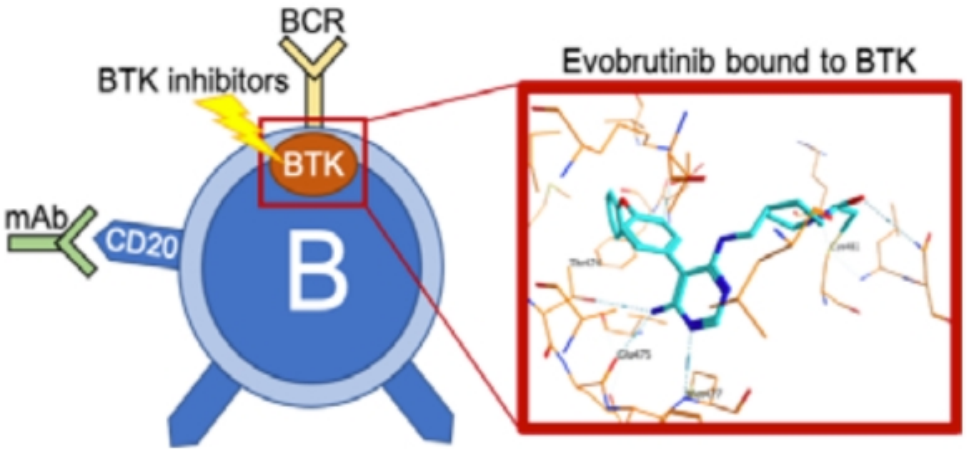
BTK MOA

- Essential kinase for the maturation of B cells together with phosphatidylinositol 3-kinase isoform p110delta (PI3Kδ).
- This pathway is important for autoimmune diseases and B-cell malignancies.
- In MS, BTK inhibitors show potential for highly specific removal of B cells.

Source: https://www.neurologylive.com/view/targeting-bruton-tyrosine-kinase-for-multiple-sclerosis-treatment /

BTK MOA

FIGURE. Comparison of Monoclonal Antibody B-Cell Therapy With BTK Inhibitors in Managing B-Cell Diseases



Source: https://www.neurologylive.com/view/targeting-bruton-tyrosine-kinase-for-multiple-sclerosis-treatment /

Evobrutinib EF

Outcome	Placebo (N = 53)	Evobrutinib, 25 mg QD (N = 50)	Evobrutinib, 75 mg QD (N = 51)	Evobrutinib, 75 mg BID (N = 53)	Dimethyl Fumarate (N = 54)
Relapse at 24 wk¶					
No. of relapses	9	13	3	2	5
Unadjusted annualized relapse rate (95% CI)‖	0.37 (0.17 to 0.70)	0.57 (0.30 to 0.97)	0.13 (0.03 to 0.38)	0.08 (0.01 to 0.30)	0.20 (0.06 to 0.47)
Relapse rate ratio (95% CI)**	NA	1.66 (0.67 to 4.09)	0.31 (0.08 to 1.20)	0.23 (0.05 to 1.09)	NA
Relapse-free status at wk 24¶					
Patients with no relapse (95% CI) — %	77 (64 to 88)	74 (60 to 85)	88 (76 to 96)	87 (75 to 95)	89 (77 to 96)
Odds ratio for no relapse (95% CI)††	NA	0.75 (0.29 to 1.95)	2.79 (0.92 to 8.41)	2.08 (0.72 to 5.99)	NA
Change from baseline in EDSS score at 24 wk¶‡‡					
Median	0.0	0.0	0.0	0.0	0.0
Range	−1.0 to 1.0	−2.5 to 2.5	−4.5 to 0.5	−0.5 to 1.0	−1.0 to 1.0

Source: https://pubmed.ncbi.nlm.nih.gov/31075187/

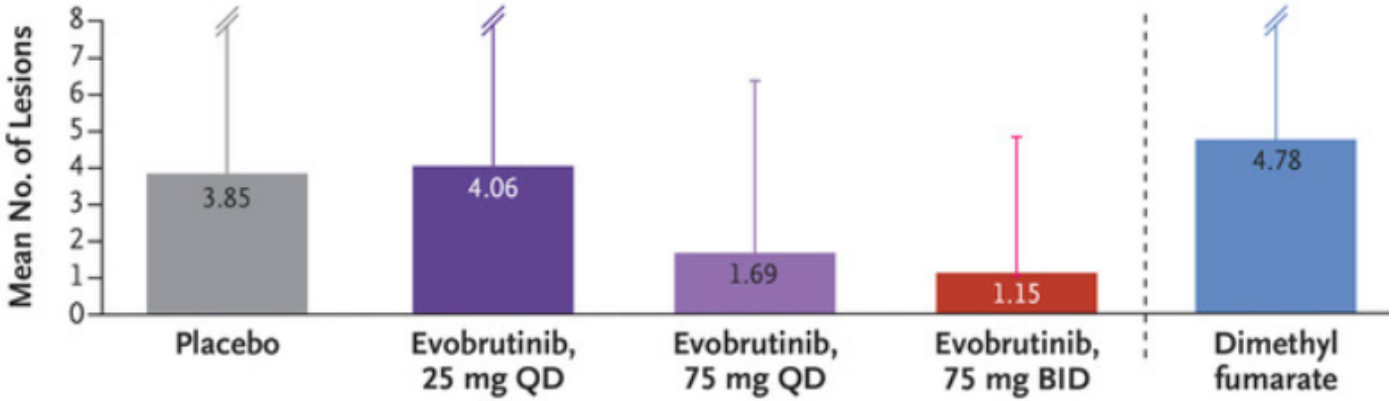
Evobrutinib EF

Outcome	Placebo (N = 53)	Evobrutinib, 25 mg QD (N = 50)	Evobrutinib, 75 mg QD (N = 51)	Evobrutinib, 75 mg BID (N = 53)	Dimethyl Fumarate (N = 54)
Cumulative no. of gadolinium-enhancing lesions on T_1-weighted MRI at 12, 16, 20, and 24 wk†					
Mean	3.85±5.44	4.06±8.02	1.69±4.69	1.15±3.70	4.78±22.05
Median	1	1	0	0	0
Range	0–20	0–38	0–27	0–25	0–160‡
Interquartile range	0–6	0–2	0–1	0–1	0–1
Lesion rate ratio (95% CI)§	NA	1.45 (0.72 to 2.91)	0.30 (0.14 to 0.63)	0.44 (0.21 to 0.93)	NA
Adjusted P value vs. placebo	NA	0.32	0.005	0.06	NA
Unadjusted P value vs. placebo	NA	0.29	0.002	0.03	NA

Source: https://pubmed.ncbi.nlm.nih.gov/31075187/

Evobrutinib EF

A Total No. of Lesions at Wk 12 through 24



Lesion rate ratio (95% CI)	1.45 (0.72–2.91)	0.30 (0.14–0.63)	0.44 (0.21–0.93)
Adjusted P value vs. placebo	0.32	0.005	0.06
Unadjusted P value vs. placebo	0.29	0.002	0.03

Source: https://pubmed.ncbi.nlm.nih.gov/31075187/

Evobrutinib SE

Adverse Event	Placebo–Evobrutinib, 25 mg QD* (N=54)	Evobrutinib, 25 mg QD (N=52)	Evobrutinib, 75 mg QD (N=53)	Evobrutinib, 75 mg BID (N=54)	Dimethyl Fumarate (N=54)
	number of patients (percent)				
Most common adverse events¶					
Nausea	0	2 (4)	0	1 (2)	3 (6)
Diarrhea	2 (4)	1 (2)	0	0	4 (7)
Nasopharyngitis	5 (9)	9 (17)	3 (6)	7 (13)	2 (4)
Upper respiratory tract infection	2 (4)	1 (2)	1 (2)	1 (2)	3 (6)
Urinary tract infection	5 (9)	2 (4)	1 (2)	0	2 (4)
Increase in alanine aminotransferase	4 (7)	3 (6)	6 (11)	5 (9)	3 (6)
Increase in aspartate aminotransferase	1 (2)	1 (2)	2 (4)	4 (7)	2 (4)
Increase in lipase	5 (9)	2 (4)	5 (9)	5 (9)	3 (6)
Increase in creatinine	1 (2)	0	3 (6)	3 (6)	1 (2)
Low lymphocyte count	0	0	0	1 (2)	5 (9)
Arthralgia	1 (2)	2 (4)	3 (6)	0	4 (7)
Headache	2 (4)	3 (6)	2 (4)	1 (2)	1 (2)
Flushing	0	0	0	0	12 (22)

Source: https://pubmed.ncbi.nlm.nih.gov/31075187/

Evobrutinib SE

Adverse Event	Placebo–Evobrutinib, 25 mg QD* (N=54)	Evobrutinib, 25 mg QD (N=52)	Evobrutinib, 75 mg QD (N=53)	Evobrutinib, 75 mg BID (N=54)	Dimethyl Fumarate (N=54)
	number of patients (percent)				
Any adverse event	30 (56)	28 (54)	35 (66)	34 (63)	35 (65)
Any grade 3 or 4 adverse event†	6 (11)	1 (2)	7 (13)	8 (15)	7 (13)
Serious adverse event‡	2 (4)	2 (4)	2 (4)	4 (7)	2 (4)
Adverse event leading to discontinuation	5 (9)	3 (6)	6 (11)	7 (13)	2 (4)
Adverse event deemed by investigator to be related to trial agent	14 (26)	10 (19)	15 (28)	18 (33)	26 (48)
Infection	16 (30)	17 (33)	10 (19)	12 (22)	12 (22)
Neoplasm§	2 (4)	0	0	0	1 (2)

Source: https://pubmed.ncbi.nlm.nih.gov/31075187/

Evobrutinib Clinical Trial

- A Phase III, Multicenter, Randomized, Parallel Group, Double Blind, Double Dummy, Active Controlled Study of Evobrutinib Compared With an Interferon Beta 1a (Avonex®), in Participants With Relapsing Multiple Sclerosis to Evaluate Efficacy and Safety
  - Phase 3 trial
    - Annualized Relapse Rate (ARR) over 96 weeks

Fenebrutinib

- The Phase III RMS Trials
  - FENhance 1
  - FENhance 2
- The Phase III PPMS Trial
  - FENtrepid
- All three trials are targeting clinical disability progression and have a primary endpoint of 12-week composite confirmed disability progression (cCDP-12)

Other Trials

DELIVER-MS

Questions?