MAYZENT®
(siponimod) tablets
0.25 mg • 2 mg

Mayzent® - FDA approval

Investor Relations

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Mayzent® a significant addition to Novartis innovative and growing neuroscience portfolio

- 1st and only treatment specifically approved for active secondary progressive multiple sclerosis (SPMS) in over 15 years[1]
- Addresses critical unmet need for Relapsing-Remitting MS (RRMS) patients in transition and SPMS patients with active disease who have transitioned
- Will not require First Dose Observation (FDO) upon treatment initiation – except for patients with pre-existing CV conditions[2]
- Approved across MS spectrum for Clinically Isolated Syndrome (CIS), RRMS and Active Secondary Progressive Disease, in adults

1. Largest trial performed in SPMS; Kappos L et al. Siponimod versus placebo in secondary progressive multiple sclerosis: a double-blinded randomized, phase 3 study. The Lancet. 2018; DOI 10.1016/S0140-6736(18)30475-6.
2. FDO is only recommended for patients with certain pre-existing cardiac conditions - sinus bradycardia, first or second-degree [Mobitz type I] AV block, or a history of myocardial infarction or heart failure.

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MS a chronic disease that attacks the central nervous system resulting in significant physical disability over time

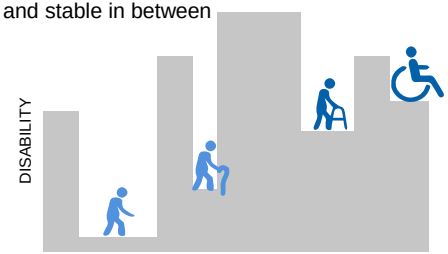
EDSS	0.0 Normal neurological exam	2.0 Minimal disability	3.0 Significant disability	4.0 Increased difficulty walking unaided	6.0 Walking aid (1 side) required	6.5 Walking aid (both sides) required	7.0 Bound to wheelchair	9.0 Bedridden

★ SPMS can begin with an EDSS 2+[4]

MS characterized by different phenotypes[1,2]

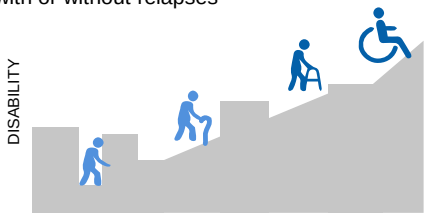
RRMS ~85%[1,2]

Acute relapses with full or partial recovery and stable in between



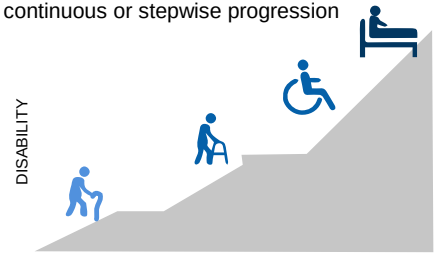
SPMS ~75-80% patients with RRMS progress to SPMS[2]

Begins as RRMS, followed by progression with or without relapses



PPMS ~15%[2]

Progression from onset; no relapses and continuous or stepwise progression



Active SPMS defined as with relapses and/or evidence of new MRI activity

MS – multiple sclerosis PPMS – primary progressive MS RRMS – relapsing–remitting MS SPMS – secondary progressive MS EDSS - Expanded Disability Status Scale. 1. National MS society. 2. Antel J *et al*. *Acta Neuropathol* 2012;123:627–38. 3. Lassmann H *et al*. *Nat Rev Neurol* 2012;8:647–56. 4. Derived from Systematic literature review (2012), Internal Market Research (2016-18) and IPSOS MS Monitor Q2 2018

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Mayzent® 1st oral DMT proven to delay disability progression and cognitive impairment where others have failed[1]

EXPAND study[2]: typical SPMS population with high unmet need (see slide 17 in backup)

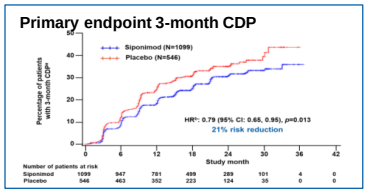
Age (mean): 48 years
Years since onset of MS (mean): 17 years
EDSS (mean/ median): 5.4 / 6.0
Relapse-free for prior 2 years (%): 64%

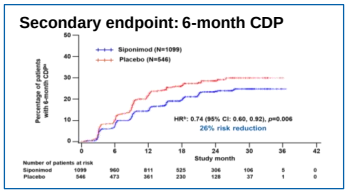
Disability progression[3]

Reduction in risk of CDP vs. placebo

21%	3-month	p<0.013	Primary end-point
26%	6-month	p<0.006	
33%	3-month	p value = 0.0100	In patients with relapse in 2 yrs prior to screening
36%	3-month	p value = 0.0277	In patients with MRI activity at baseline

The effect on CDP was consistent across the patient subgroups





Confirmed relapses

55% reduction ARR[3] vs. placebo (p < 0.0001)

Cognition

SDMT[2]: 2.48 points improvement from baseline, vs. placebo[3] (p<0.0004)

Brain volume loss

23.4% reduction in brain volume loss vs. placebo[3] (p = 0.0002)

ARR – annualized relapse rate CDP - confirmed disability progression. EDSS - Expanded Disability Status Scale. DMT – Disease modifying treatment. 1. Natalizumab failed trial to demonstrate delay in disability progression. Kapoor R, et al. Lancet Neurol. 2018;17:405-15 (composite endpoint included time to EDSS progression, 20% increase in timed 25 foot walk or 20% increase in 9-hole peg test). 2. Largest trial performed in SPMS; SDMT – Symbol Digit Modalities Test. 3. Kappos L et al. Siponimod versus placebo in secondary progressive multiple sclerosis: a double-blinded randomized, phase 3 study. The Lancet. 2018; DOI 10.1016/S0140-6736(18)30475-6

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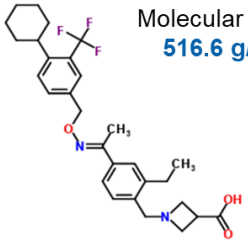
Mayzent® a highly selective brain penetrant $S1P_{1,5}$ modulator with superior PK and lower heart rate effects vs. other compounds in the class

S1P receptor modulators profiles[7]



Molecular weight
516.6 g/mol

An oral, highly selective $S1P_{1,5}$ receptor modulator[1]

- Exerts anti-inflammatory effects by blocking $S1P_1$-dependent egress of T and B lymphocytes from lymphoid organs[2,3]
- Readily crosses the blood-brain barrier[4]
- Preclinical evidence suggests central anti-inflammatory as well as neuroprotective/ remyelinating properties of Mayzent®, potentially through $S1P_5$[5,6]

	Mayzent® (siponimod)	Gilenya® (fingolimod)	Ozanimod
Receptor selectivity	$S1P_{1,5}$	$S1P_{1,3,4,5}$	$S1P_{1,5}$
Activity of metabolites	Negligible	Fingolimod-P; active at S1PRs	Metabolites, active at S1PRs
Elimination half life of parent compound (hours)[7]	30h	180h	19h; (CC-112273; 10-13 days[8])
HR reduction upon treatment initiation	Dose titration over 5d -3bpm @day7	(no titration) -7.4bpm @4-5h	Dose titration over 7d -5-8bpm nadir @day8

Gilenya® is approved for RMS for adults and pediatric patients, PPMS study did not meet the primary end point S1P1,5, sphingosine 1-phosphate receptors subtypes 1 and 5 1. Gergely P, et al. Br J Pharmacol. 2012;167:1035–1047, 2. Bar-Or A, et al. Mult Scler. 2017;23:P1238, 3. Seabrook TJ, et al. Mult Scler. 2010;16:P858, 4. Briard E, et al. ChemMedChem. 2015;10:1008–1018, 5. Mannioui A, et al. Mult Scler. 2017 [Epub ahead of print], 6. Gentile A, et al. J Neuroinflammation. 2016;13:207. 7. Juif PE, et al. Expert Opin Drug Metab Toxicol. 2016;12:879–895. 8. Disclosed at Celgene Q1 2018 Investors Call, May 4th, 2018

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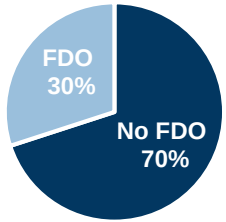
US: FDA approved label – selected information (1/2)

Indication	**Mayzent® is indicated for the treatment of relapsing forms of multiple sclerosis, to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults**
Posology	▪ No First Dose Observation (FDO), except for those patients with certain pre-existing cardiac conditions [heart rate <55 1st or 2nd degree AV block (Mobitz I), or a history of myocardial infarction or heart failure] ▪ Prior to treatment initiation, genotype (CYP2C9) testing is required to define the daily maintenance dose: - 2mg (CYP2C9 *1*1, *2*2, *1*2; ~94.5% of population) - or 1mg (CYP2C9 *1*3 or *2*3; ~5% of population) ▪ Treatment up-titration for 5 days (for 2mg maintenance dose) or 4 days (for 1mg maintenance dose) ▪ Contraindicated in: - Patients with a CYP2C9*3/*3 genotype (0.5% of population) - Patients who in the last 6 months experienced myocardial infarction, unstable angina, stroke, TIA, decompensated heart failure requiring hospitalization, or Class III/IV heart failure - Patients with Mobitz II 2nd, 3rd degree AV block, or sick sinus syndrome, unless patient has a functioning pacemaker

Estimated % patients requiring FDO
~70% Mayzent® patients require No FDO



Personalized on-boarding
Pre-initiation

- **Easy CYP2C9 genotype test** completed by most commercial and hospital labs
- Estimated cost USD 200-250

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US: FDA approved label – selected information (2/2)

Clinical

Evidence demonstrated in patients with SPMS:

- 21% reduction in risk of 3-month confirmed disability progression (CDP) vs. placebo (p<0.013)
- Although Mayzent® had a significant effect on disability progression compared to placebo in patients with active SPMS (e.g., SPMS patients with an MS relapse in the 2- years prior to the study), the effect of Mayzent® in patients with non-active SPMS was not statistically significant.
- Secondary end points:
  - 55% reduction in Annualized Relapse Rate (ARR) vs. placebo (nominal p < 0.0001)
  - 79% less increase in T2 lesion volume vs. placebo (nominal p<0.0001)
  - No significant reduction in time to 3-month confirmed worsening from baseline in the timed 25-foot walk
  - Point estimates of all listed subgroups analyses favor Mayzent®

Safety

- Most common adverse reactions (incidence greater than 10%): headache, hypertension, transaminase increased and falls.
- Overall, Adverse Drug Reactions list (e.g. infections, macular edema, blood pressure) in line with Gilenya® label.
- Re-titration in case a dose is missed during the titration period or when 4 consecutive doses are missed during maintenance.

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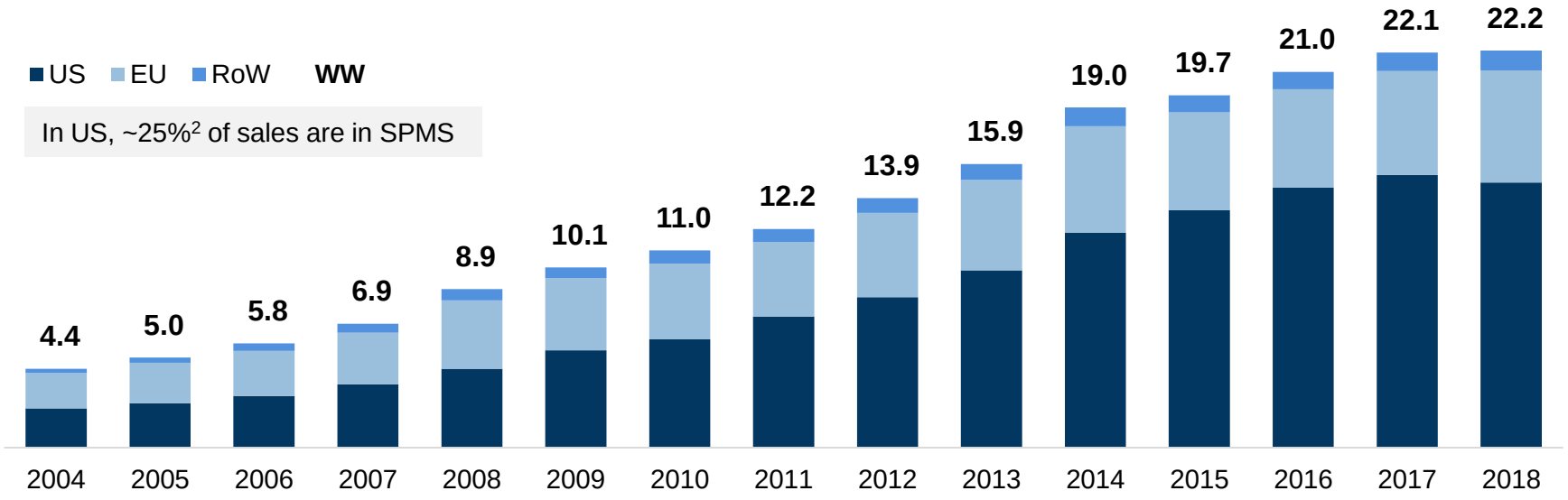
USD 22bn MS worldwide market[1] with a large unmet need in SPMS[2]

Value

USD billion



1. Source: Evaluate Pharma- Mar'19. 2. Due to lack of an FDA approved oral treatment for SPMS

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For MS patients when progression becomes noticeable, Mayzent® can deliver hope & independence longer

RRMS patients in transition and patients with active secondary progressive disease

- Symptoms worsen and don't return to baseline
- Irreversible loss of physical and cognitive function, independent of relapses

Patient characteristics	▪ ~40 years of age ▪ Diagnosed with MS for >5 years
Physical state	▪ Impact on walking ability, increasingly require aid ▪ Fatigue on exertion ▪ Flickering and blurred vision ▪ Numbness and tingling in feet and hands ▪ Cognitive fog and concentration issues
Impact of disease	▪ Employment scaled back and social, family life impacted ▪ Increasing dependence on care partners and adaption to environment

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Mayzent® focuses on patients with the highest unmet need

Target patient

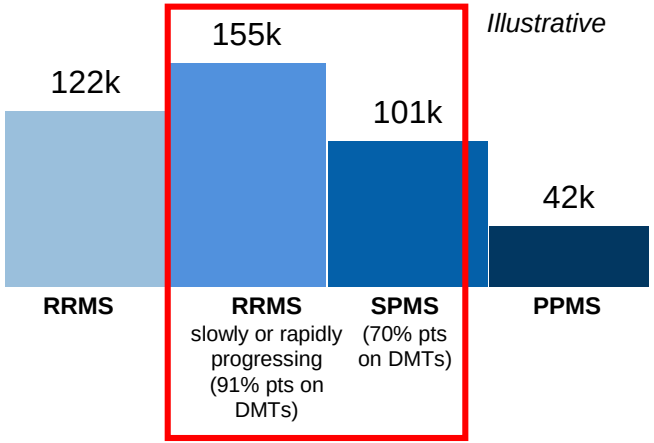
MS patients when progression becomes noticeable regardless of relapses

RRMS patients in transition

Patients w/active secondary progressive disease

Mayzent® US targeting ~250k patients

US diagnosed MS patients – RRMS with progression or diagnosed SPMS



Total 420k MS patients

US MS switch rate dynamics by phenotype each year[2]

RRMS: 20%
SPMS: 23%

Sources: Q1 2019 Spherix Real World Dynamics (RRMS includes 11% of CIS pts); *2019 MS Therapy Monitor Ipsos - % RRMS pts progression with known EDSS score 3+ and known stated disability progression (56%) – Q4 2018
1. Spherix Q1 '19 RealTime Dynamics MS Report 2. Spherix Q1 '19 MS RWD Switch Report – RRMS and aSPMS – HCP reporting of % of MS patients being treated with DMTs they have switched (for any reason) to a different DMT

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Mayzent® provides outstanding value at no additional cost in US

- Mayzent® is priced in-line with other MS treatments at an annual list price of USD 88,500
- Pricing aligns very well with that of existing high efficacy DMTs and with payer expectations
- Mayzent® will be available to patients in the US within one week

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Mayzent® submissions completed in key markets with regulatory action dates expected throughout 2019 onward

Selected submissions for Mayzent®

NDA approval
March 26, 2019

MAA validated

Decision expected latest Dec 2019

Fast track designation granted

Q4 2018 submission

Decision expected Q3/Q4 2019

Q4 2018 submission

Decision expected Dec 2019

Jan 2019 submission*

Decision expected Q3/Q4 2019

Q4 2018 submission

Decision expected Q1 2020

*ODD designation granted

A significant addition to Novartis Neuroscience, focusing on a critical unmet need in MS

- Broad MS spectrum
- Unique efficacy in patients with greatest unmet need
- Safety and tolerability established in clinical studies
- Ease of patient onboarding

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Back-up

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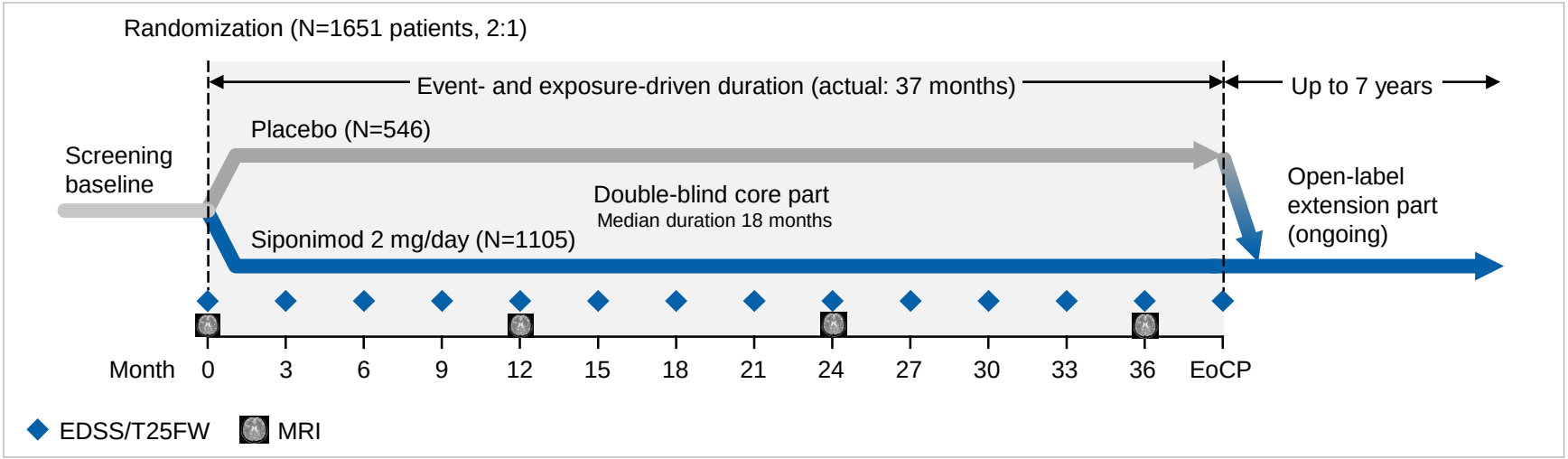
EXPAND: The largest Ph3 study in a typical SPMS population

Randomized, double-blind, placebo-controlled, event- and exposure-driven study[1]



EXPAND study was conducted across 31 countries and 292 sites

EoCP, end of core part; EDSS, expanded disability status scale; T25FW, timed 25-foot walk

1. Kappos L, et al. Lancet. 2018;391:1263-73.

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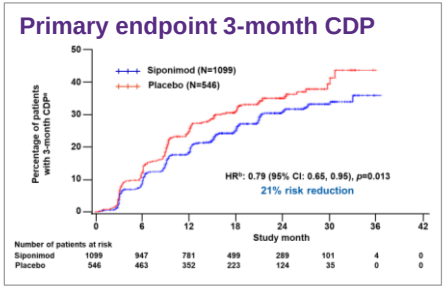
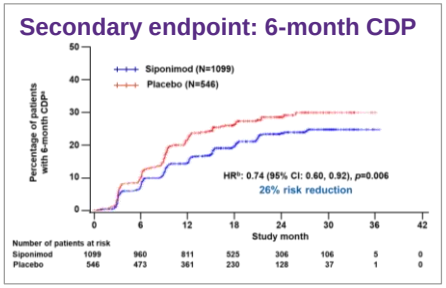
EXPAND Ph3 population is typical SPMS and significantly differs from the other RMS trials

	SPMS	Recent RMS trials (2010-2015)		
Patient characteristics	**EXPAND[1] Siponimod**	**Key differences SPMS vs RMS Studies**	**DEFINE[2] DMF**	**CARE-MS II[3] Alemtuzumab**	**FREEDOMS[4] Fingolimod**
Number of patients	1651		1237	840	1272
Age, years (mean)	48	**Older, longer MS duration**	38	35‡	37
Time since onset, years (mean)	17		5.6#	5	8
EDSS (mean/median)	5.4/6.0	**More Disabled**	2.4/n.r.#	2.7/2.5‡	2.4/2.0
EDSS ≥ 6.0 (%)	56		0&	0&	0&
Timed 25-foot walk test, mean (sec)	16.7		n.r.	n.r.	6.1
% of patients with Gd+ lesions	21	**Less inflammation**	n.r.	42‡	38
T2 lesion load, mean (cm^3)	15		n.r.	6‡ (median)	6
Relapse-free for prior 2 years, (%)	64		0&	1&	0&
On-study relapses (% in comparator group)	19§		46$*	53$	54§
On-study ARR (comparator group)	0.16§		0.36$	0.52$	0.40§

ARR – annualized relapse rate EDSS – Expanded Disability Status Scale Gd+ - gadolinium-enhancing DMF – Dimethyl fumarate 1. Kappos L, et al. Lancet. 2018;391:1263-73.; 2. Gold R, et al. N Engl J Med. 2012;367:1098-107.; 3. Coles AJ, et al. Lancet. 2012;380:1829-39.; 4. Kappos L, et al. N Engl J Med. 2010;362:387-401. §placebo comparator; $IFN β-1a comparator; ‡alemtuzumab 12 mg arm only; #Twice daily BG-12 arm only; &based on inclusion criteria; *at 2 years

EXPAND data suggest meaningful efficacy of Mayzent® on a variety of measures relevant for SPMS[1,2]





	Reduction vs placebo	p value
Physical disability outcomes		
Time to 25 Feet Walk: 3-month confirmed ≥20% worsening	6.2%	0.4398
MS Walking Scale-12 (PRO)[a]	39.7%	0.0571
Cognitive disability outcomes		
Change from baseline in Symbol Digit Modalities Test (SDMT)[d]	2.48	0.0004
Risk of 6-month confirmed worsening of ≥4 points on SDMT (post-hoc)	25.3%	0.0163
Acute clinical relapses		
Annualized relapse rate	55.5%	<0.0001
Brain imaging outcomes*		
Change from baseline in T2 Lesion Volume*	79.1%	<0.0001
Number of Gd+ lesions/per scan[b]	86.3%	<0.0001
Number of new or newly enlarging T2 lesions[c]	80.6%	<0.0001
Percent brain volume change[c]	23.4%	0.0002

CI – confidence interval CDP – confirmed disability progression HR – hazard ratio Gd+ - gadolinium-enhancing SDMT – Symbol Digit Modalities Test T2LV – T2 lesion volume T25FW – timed 25-foot walk test

1. Kappos L, et al. *Lancet* 2018; 391:1263-73. 2. Data on file Primary analysis: time to 3-month CDP on Full Analysis Set (FAS) without imputation for missing data. FAS – all treated patients analyzed according to randomization [a]Difference in change from baseline in adjusted means; [b]Cumulative number of Gd-enhancing T1 lesions per scan up to and including Month 24, Cox proportional hazards model with treatment, country/region, baseline EDSS, and SPMS group (with/without superimposed relapses, baseline definition) as covariates. [c]Average change over Months 12 and 24, relative to previous scan; [d]Difference in change from baseline in adjusted means over Month 12 and 24

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Mayzent® the only DMT that demonstrated efficacy in a typical SPMS population

Typical SPMS

	EXPAND[1] Mayzent®	ASCEND[2] natalizumab	N.American[3] IFNB1b study	European[4] IFN1b study
Number of patients	1651	887	939	718
Age, years (mean)	48	47	47	41
Time since onset, years (mean)	17	17	15	13
EDSS (mean/median)	5.4/6.0	5.6/6.0	5.1/n.r.	5.2
On-study ARR (placebo group)	0.16	0.17	0.28	0.64
Primary endpoint	3mCDP: 21%↓ (p=0.0130) 6mCDP: 26%↓ (p=0.006)	Composite[2]: OR 0.86 (p=0.287) [6mCDP: OR 1.06 (p=0.753)]	6mCDP; hazard ratio not reported, p=0.71	3mCDP, OR 0.65, p=0.0008

Younger patients, shorter disease duration, higher relapse rate

CDP – confirmed disease progression OR – odds ratio ARR – annualized relapse rate EDSS – Expanded Disability Status Scale Gd+ - gadolinium-enhancing n.r – not reported IFNB1b – interferon-beta1b

1. Kappos L, et al. Lancet. 2018;391:1263-73.; 2. Kapoor R, et al. Lancet Neurol. 2018;17:405-15 (composite endpoint included time to EDSS progression, 20% increase in timed 25 foot walk or 20% increase in 9-hole Peg test)
3. Panitch H, et al. Neurology. 2004;63:1788-95. 4. European study group Lancet. 1998;352(9139):1491–7.

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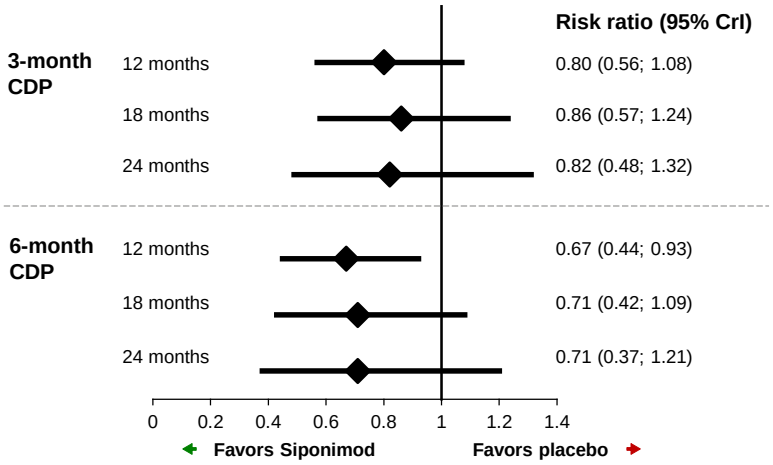
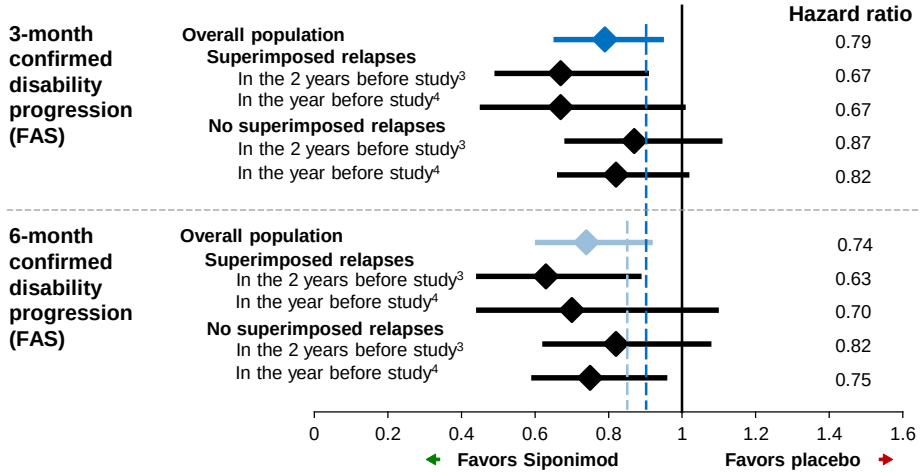
Additional analysis: disentangling the effect on disability progression from relapses[1]

Mayzent® efficacy in EXPAND was largely independent of relapses

During the study[2]



Before the study



CrI – credibility interval n/N': n=number of subjects with events/N'=number of subjects included in the population FAS – full analysis set

1. Reference: B Cree, et al. Progressive MS Therapies and Age-Dependent Factors in MS Therapy Session S8.005 (April 22, 2018), AAN Los Angeles 2. Patients who would not relapse over the specified period of time on-study regardless of treatment assignment. 3. Definition as per EXPAND protocol 4. Definition as proposed by Lublin F, et al. *Neurology.* 2014;83:278–286.

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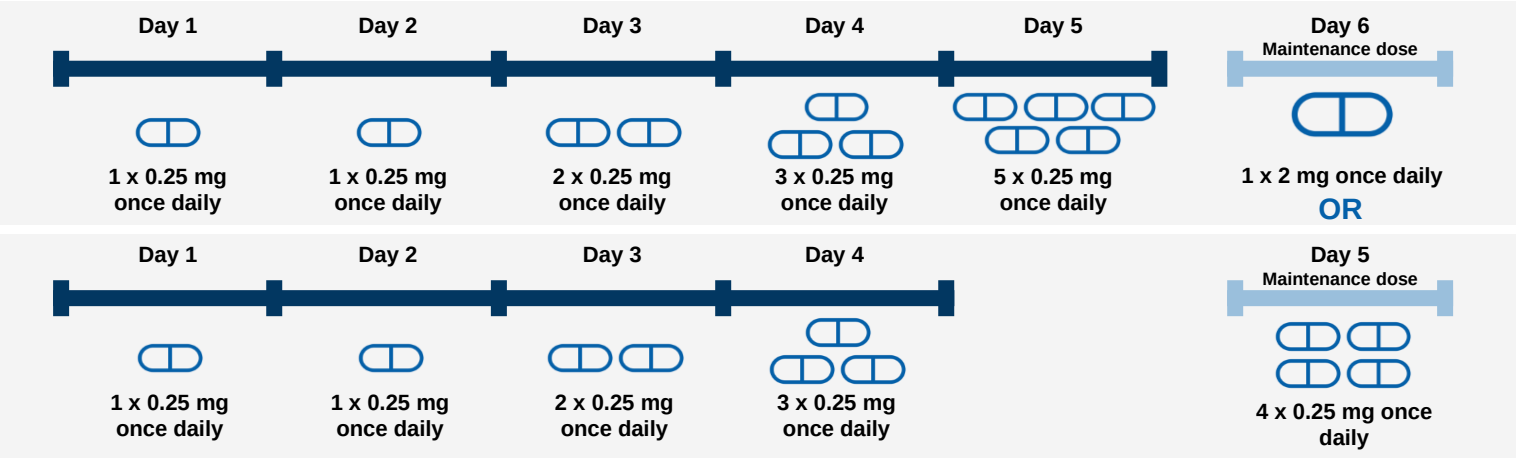
Mayzent® dose titration scheme efficiently mitigates S1P modulator-induced bradycardia

Dosing

Dose titration scheme efficiently mitigates bradycardia (a known effect associated with S1P modulators) at treatment initiation[1–4]

- Siponimod can be safely initiated with a 4 or 5-day dose titration (depending on maintenance dose, set according to the CYP2C9 status) in patients with no cardiac conditions*
- Siponimod dose re-titration is required if four or more consecutive daily doses are missed[5]
- Overall safety profile is clinically manageable[6]



*In patients with sinus bradycardia (HR <55 bpm), first or second-degree [Mobitz type I] AV block, or a history of myocardial infarction or heart failure, first dose monitoring should be conducted for a period of 6 hours for signs and symptoms of bradycardia (FDA label) 1. Gergely P, et al. Br J Pharmacol 2012;167:1035–1047. 2. Koyrakh L, et al. Am J Transplant 2005;5:529-536. 3.DiMarco JP, et al. Mult Scler Relat Disord 2014;3:629-638. 4.Legangneux E, et al. Clin Ther 2016;38:631-645. 5.Legangneux E, et al. Br J Clin Pharmacol 2013;75:831-841. 6.Kappos L, et al. Lancet 2018;391:1263–1273.

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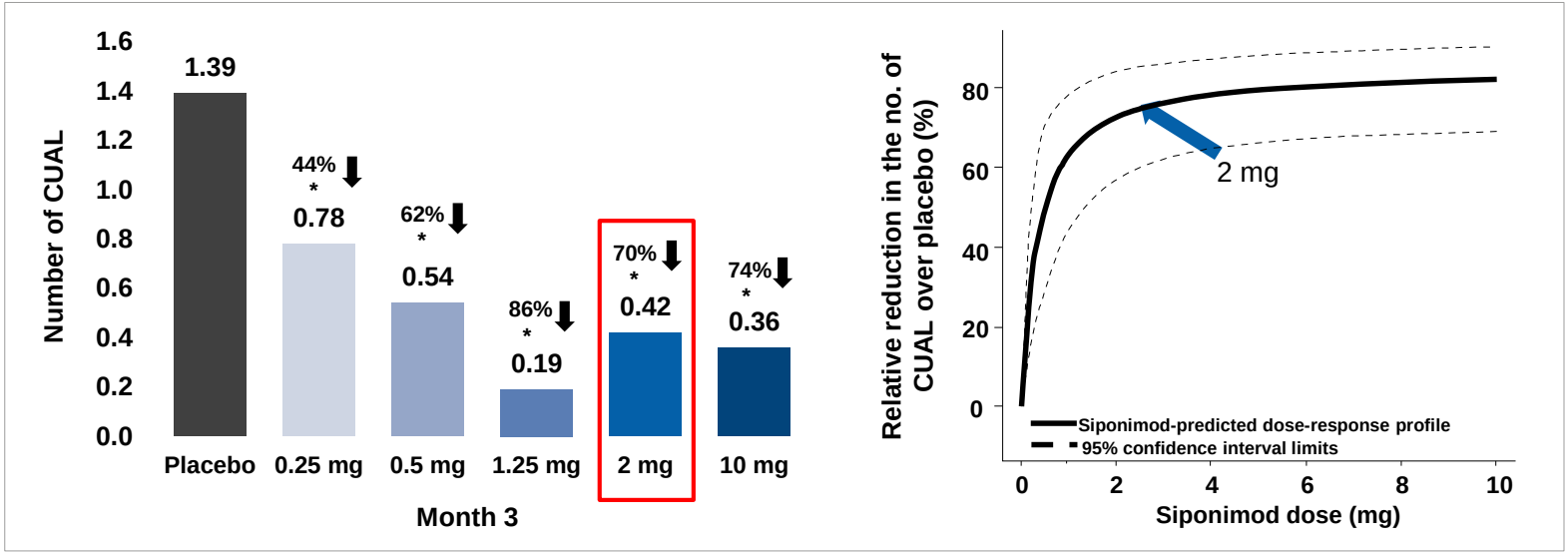
BOLD study data in patients with RRMS provided the rationale for Mayzent® dose choice in the EXPAND study

Siponimod treatment dose dependently reduces the number of CUAL[1]



*p<0.05 vs. placebo. Siponimod 2 mg is the current therapeutically relevant dose for multiple sclerosis. 1. CUAL, combined unique active lesions, defined as new Gd-enhanced lesions on T1-weighted, or new or enlarging lesions on T2-weighted MRI scans, without double counting; MRI, magnetic resonance imaging; RRMS, relapsing–remitting multiple sclerosis Selmaj K *et al. Lancet Neurol* 2013;12:756–67.

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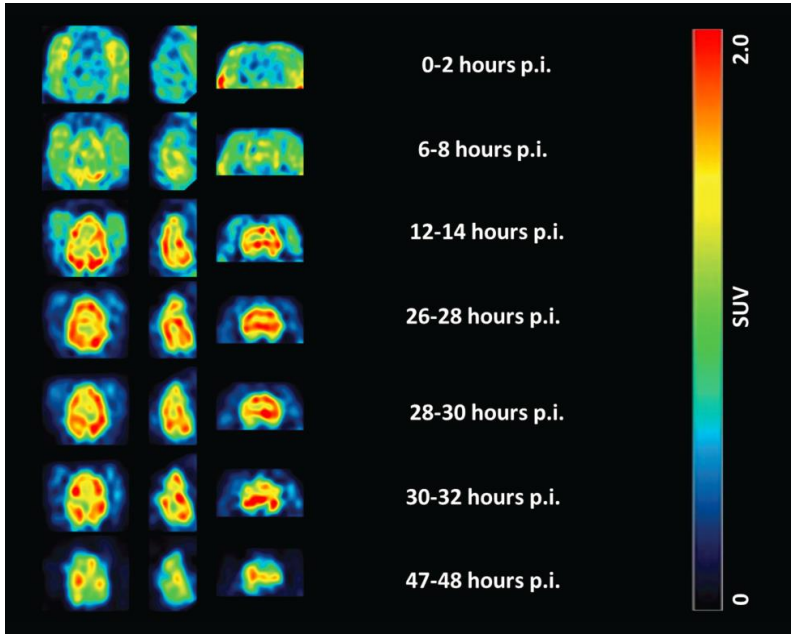
Mayzent® provides strong brain penetration



lTavares A, et al. Neurology. 2014;82(Suppl10):168; Tamagnan et al; Mult Scler. 2012;18(10 S4):[Abstract P839].