once-daily ZEPOSIA® (ozanimod) | 0.92 mg capsules

For your patients with relapsing forms of multiple sclerosis (MS)[1]...

FOCUS ON WHAT COUNTS

- **Powerful Efficacy** in Reducing ARR, GdE Lesions, and New/Enlarging T2 Lesions vs Avonex[1a]
- **Data on Brain Volume and Cognitive Processing Speed (SDMT)** in Secondary, Exploratory Endpoints and Post Hoc Analysis[2,3]
- **Safety Profile Comparable to Avonex in Overall Incidence of Adverse Reactions**[1b] ≥90% of Patients Treated With ZEPOSIA Stayed on Therapy Through Completion of Pivotal Trials[c]

[a]**Study designs:** SUNBEAM (1 year; N=1346) and RADIANCE (2 years; N=1313) were multicenter, randomized, double-blind, double-dummy, active treatment-controlled studies of daily oral ozanimod 0.46 mg (not approved for maintenance dose) or 0.92 mg vs weekly Avonex (interferon beta-1a), 30-µg intramuscular injection. **Primary endpoint:** ZEPOSIA reduced ARR vs Avonex by 48% at 1 year (0.18 vs 0.35, respectively) and by 38% at 2 years (0.17 vs 0.28, respectively). **Secondary endpoints:** ZEPOSIA reduced the number of new or enlarging T2 lesions by 48% at 1 year and by 42% at 2 years and reduced the number of GdE lesions vs Avonex by 63% at 1 year and 53% at 2 years. 9 of 10 patients showed no confirmed 3-month disability progression. There was no significant difference in 3-month confirmed disability between ZEPOSIA and Avonex.[1-3]

[b]**Adverse reactions:** Overall incidence of adverse reactions for ZEPOSIA vs Avonex at 1 year was 59.8% and 75.5%, respectively, and at 2 years was 74.7% and 83.0%, respectively. Across 2 head-to-head trials, the most common adverse reactions with an incidence of at least 2% in patients treated with ZEPOSIA and at least 1% greater than Avonex, respectively, were as follows: upper respiratory infection, 26% (vs 23%); hepatic transaminase elevation, 10% (vs 5%); orthostatic hypotension, 4% (vs 3%); urinary tract infection, 4% (vs 3%); back pain, 4% (vs 3%); hypertension, 4% (vs 2%); and abdominal pain upper, 2% (vs 1%). Data are not an adequate basis for comparison of rates between ZEPOSIA and the active control. Upper respiratory infection includes nasopharyngitis, upper respiratory tract infection, pharyngitis, respiratory tract infection, bronchitis, rhinitis, respiratory tract infection viral, viral upper respiratory tract infection, rhinorrhea, tracheitis, and laryngitis. Hepatic transaminase elevation includes alanine aminotransferase increased, gamma-glutamyl transferase increased, aspartate aminotransferase increased, hepatic enzyme increased, liver function test abnormal, and transaminase increased. Hypertension includes hypertension, essential hypertension, and orthostatic hypertension. Overall discontinuation rates for ZEPOSIA vs Avonex at 1 year were 6% and 8%, respectively, and at 2 years were 10% and 15%, respectively. Discontinuation rates due to adverse reactions for ZEPOSIA vs Avonex at 1 year were 2.9% and 3.6%, respectively, and at 2 years were 3.0% and 4.1%, respectively. **Serious infections:** The rate of serious infections at 1 year for ZEPOSIA was 1.1% vs 0.7% for Avonex and the rate at 2 years for ZEPOSIA was 0.9% vs 0.9% for Avonex. **Malignancy rates:** The rate of malignancies at 1 year for ZEPOSIA was 0.2% vs 0% for Avonex and the rate at 2 years for ZEPOSIA was 0.9% vs 0.5% for Avonex.[1-3]

[c]In the 1-year SUNBEAM trial, 94% of patients who received ZEPOSIA (n=447) and 92% who received Avonex (n=448) completed the study. In the 2-year RADIANCE trial, 90% of patients who received ZEPOSIA (n=433) and 85% who received Avonex (n=441) completed the study.

ARR=annualized relapse rate; GdE=gadolinium enhancing; SDMT=Symbol Digit Modalities Test.

Indication

ZEPOSIA is indicated for the treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults.

IMPORTANT SAFETY INFORMATION

Contraindications:

- Patients who in the last 6 months, experienced myocardial infarction, unstable angina, stroke, transient ischemic attack (TIA), decompensated heart failure requiring hospitalization, or Class III/IV heart failure or have a presence of Mobitz type II second or third-degree atrioventricular (AV) block, sick sinus syndrome, or sino-atrial, unless the patient has a functioning pacemaker
- Patients with severe untreated sleep apnea
- Patients taking a monoamine oxidase (MAO) inhibitor

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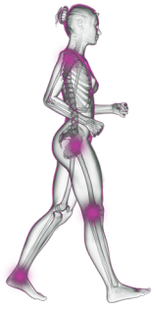
Bristol Myers Squibb™

Both Cognitive Impairment and Physical Disability Can Play a Prevalent Role in the Lives of Patients With MS[4-9]



The Impact of MS on Physical Function Is Well Established

- **Up to 80% of patients** with MS will experience some form of physical disability within 10 to 15 years of their diagnosis[4]

Mobility Impairment Is Common

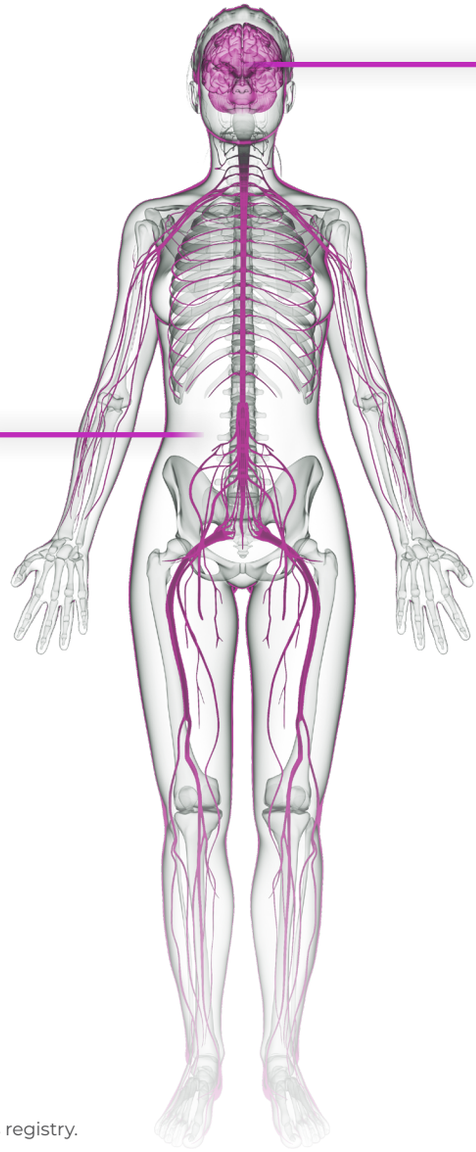
- Physical symptoms associated with MS include difficulty walking, muscle weakness, balance problems, and spasticity—which can impact the patient's ability to work and participate in social events[4,5]

In a 2013 study of **27,918 patients in the NARCOMS registry**[6]**:**

45% of patients with MS between the ages of 18 and 64 needed a mobility device to help them walk

50% of patients said they had difficulty with daily activities 15 years after diagnosis

NARCOMS=North American Research Committee on Multiple Sclerosis registry.

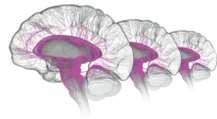


A 5-year prospective cohort study (N=650; 520 with relapse-onset MS, 130 healthy controls) **found**[10]**:**

≈3x more MS-specific **whole brain volume loss**[a]

≈10x more MS-specific **thalamic volume loss**[a]

in younger adult MS patients (30 years old) vs older MS patients (60 years old)



BVL May Be Correlated With Cognitive Disability[8,11,12]

Volume loss of the whole brain and of the thalamus (a grey matter structure) have been correlated with cognitive decline, which can impact patients' lives

Cognitive Decline Is a Common Feature of MS

- Research has shown that cognitive disability can affect **up to 65% of patients** with MS[9]

DMTs are not intended for use in MS symptom management.

IMPORTANT SAFETY INFORMATION (CONTINUED)

Infections: ZEPOSIA may increase the susceptibility to infections. Life-threatening and rare fatal infections have occurred in patients receiving ZEPOSIA. Obtain a recent (i.e., within 6 months or after discontinuation of prior MS therapy) complete blood count (CBC) including lymphocyte count before initiation of ZEPOSIA. Delay initiation of ZEPOSIA in patients with an active infection until the infection is resolved. Consider interruption of treatment with ZEPOSIA if a patient develops a serious infection. Continue monitoring for infections up to 3 months after discontinuing ZEPOSIA

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Robust Data From 2 Pivotal Trials (N=2659) and an Ongoing Open-Label Extension Study[1-3,13]

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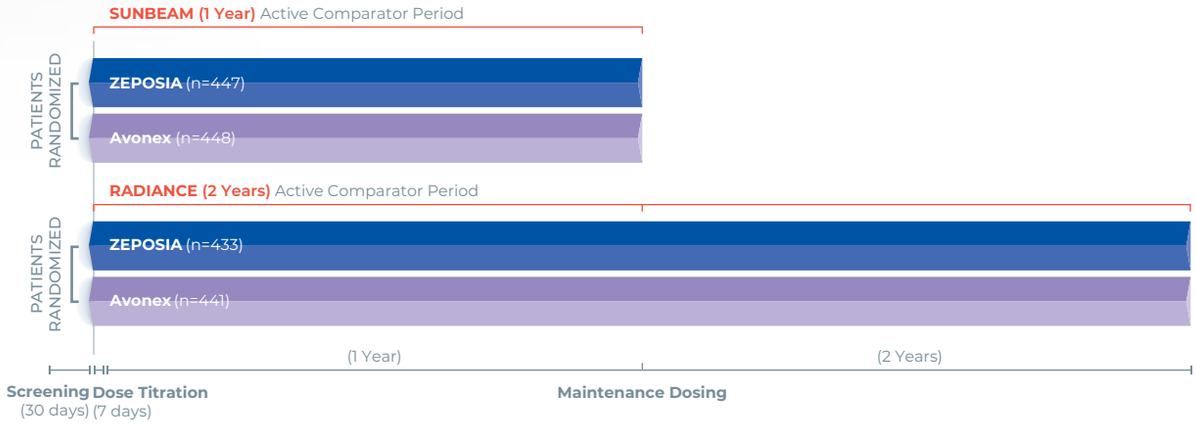
The Largest Number of Patients With RMS Studied in Pivotal Head-to-Head Trials With an Active Comparator (N=2659)[2,3a]

Study Design for Pivotal Trials[2,3]

SUNBEAM (1 Year) **and RADIANCE** (2 Years)



Study Endpoints[1]

PRIMARY

- Annualized Relapse Rate

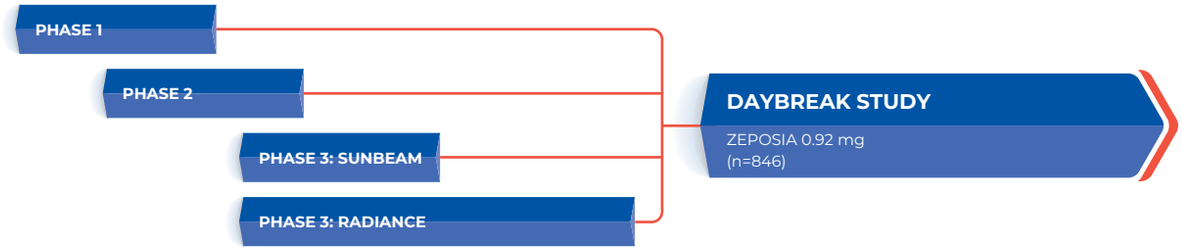
KEY SECONDARY

- GdE Lesions
- New/Enlarging T2 Lesions
- Confirmed Disability Progression

View **MOA**

Study Design for Open-Label Extension[13b]

DAYBREAK (Up to 3 Years)[c]



Study Endpoints[13]

PRIMARY

- Long-Term Safety

KEY SECONDARY

- Annualized Relapse Rate
- GdE Lesions
- New/Enlarging T2 Lesions

- The patient population evaluated in this analysis included those who received ZEPOSIA 0.92 mg (n=846) and completed the randomized Phase 1, 2, or 3 trials[13]
- Endpoints were analyzed descriptively in the DAYBREAK study[13]

[a]2659 patients includes all 3 arms of the study: the 0.92-mg dose of ZEPOSIA, the 0.46-mg dose of ZEPOSIA (not approved for maintenance dose), and the 30-µg dose of Avonex.[2,3]
[b]DAYBREAK is an ongoing open-label extension (OLE) trial that enrolled participants from multiple randomized phase 1 to 3 studies, including SUNBEAM and RADIANCE, and is presented as an interim analysis with a data cutoff of December 20, 2019.
[c]Study period includes DAYBREAK Day 1 through last treatment date or the data-cutoff date.

RMS=relapsing multiple sclerosis.

IMPORTANT SAFETY INFORMATION (CONTINUED)

Infections (Continued):

- Herpes zoster was reported as an adverse reaction in ZEPOSIA-treated patients. Herpes simplex encephalitis and varicella zoster meningitis have been reported with sphingosine 1-phosphate (S1P) receptor modulators. Patients without a healthcare professional-confirmed history of varicella (chickenpox), or without documentation of a full course of vaccination against varicella zoster virus (VZV), should be tested for antibodies to VZV before initiating ZEPOSIA. A full course of vaccination for antibody-negative patients with varicella vaccine is recommended prior to commencing treatment with ZEPOSIA

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ZEPOSIA Delivered Powerful Efficacy in Reducing ARR vs Avonex in Pivotal Trials[1]

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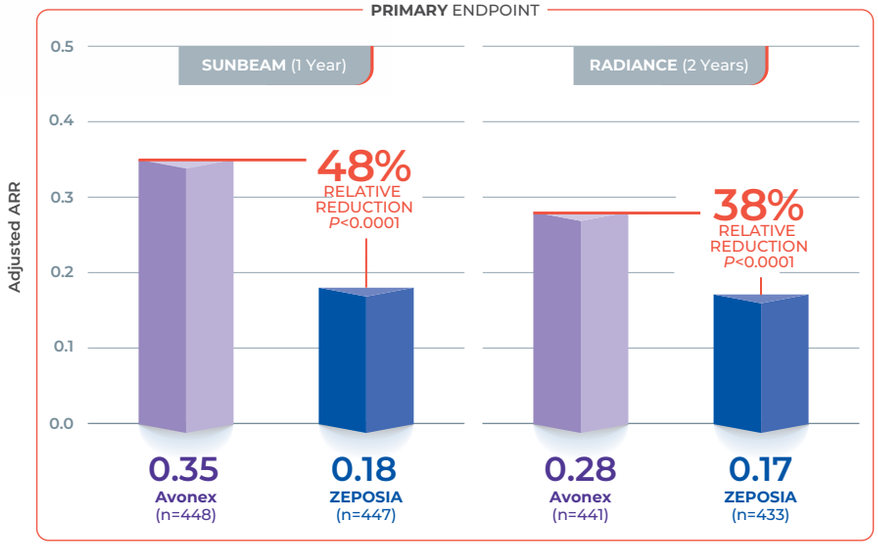
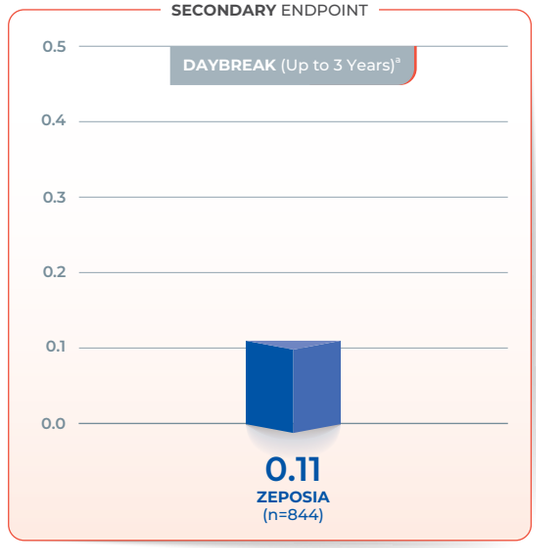
In the Open-Label Extension Study, Patients Treated With ZEPOSIA Up to 3 Years[a] Had an ARR of 0.11[13]

ARR in Pivotal Trials[1]



ARR in OLE[13]



[a]Study period includes DAYBREAK Day 1 through last treatment date or the data-cutoff date.

A relapse was defined as the occurrence of new or worsening neurological symptoms persisting for more than 24 hours attributable to MS and immediately preceded by a relatively stable or improving neurological state of at least 30 days.

DAYBREAK is an ongoing open-label extension trial that enrolled participants from multiple randomized phase 1 to 3 studies, including SUNBEAM and RADIANCE, and is presented as an interim analysis with a data cutoff of December 20, 2019. Endpoints were analyzed descriptively.[13]

IMPORTANT SAFETY INFORMATION (CONTINUED)

Infections (Continued):

- Cases of fatal cryptococcal meningitis (CM) were reported in patients treated with another S1P receptor modulator. If CM is suspected, ZEPOSIA should be suspended until cryptococcal infection has been excluded. If CM is diagnosed, appropriate treatment should be initiated.
- Progressive Multifocal Leukoencephalopathy (PML) is an opportunistic viral infection of the brain that typically occurs in patients who are immunocompromised, and that usually leads to death or severe disability. No cases of PML were identified in active-controlled MS clinical trials with ZEPOSIA. PML has been reported in patients treated with S1P receptor modulators and other MS therapies and has been associated with some risk factors. If PML is suspected, withhold ZEPOSIA and perform an appropriate diagnostic evaluation. If confirmed, treatment with ZEPOSIA should be discontinued
- In clinical studies, patients who received ZEPOSIA were not to receive concomitant treatment with antineoplastic, non-corticosteroid immunosuppressive, or immune-modulating therapies used for treatment of MS. Concomitant use of ZEPOSIA with any of these therapies would be expected to increase the risk of immunosuppression. When switching to ZEPOSIA from immunosuppressive medications, consider the duration of their effects and their mode of action to avoid unintended additive immunosuppressive effects
- Use of live *attenuated* vaccines should be avoided during and for 3 months after treatment with ZEPOSIA. If live *attenuated* vaccine immunizations are required, administer at least 1 month prior to initiation of ZEPOSIA

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Proven Superior vs Avonex in Reducing Lesions Across All Secondary Measures of MRI Activity[1]

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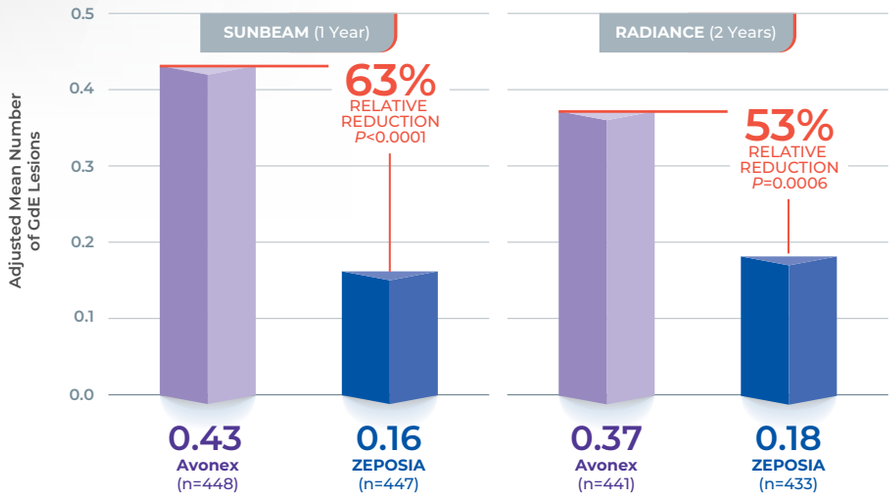
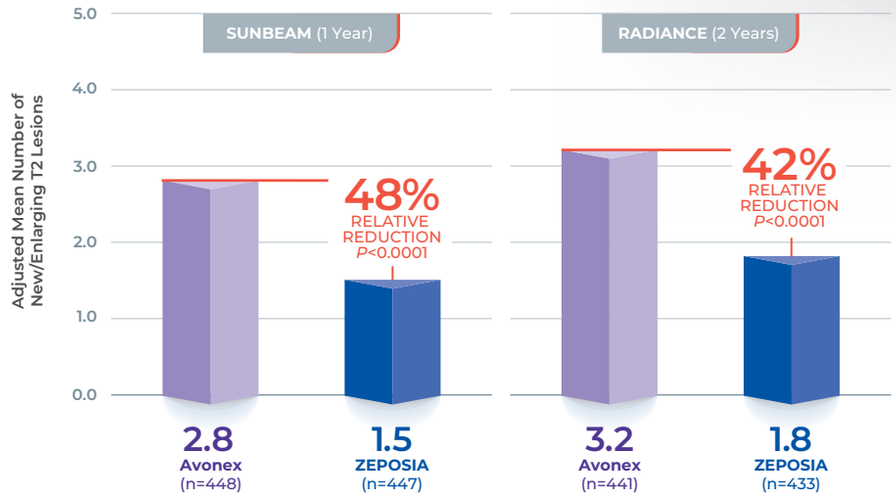
SECONDARY ENDPOINT — **Number of GdE Lesions**



SECONDARY ENDPOINT — **Number of New/Enlarging T2 Lesions**



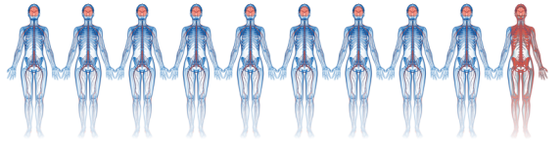
View **OLE Data**

In the 1-year SUNBEAM study, brain MRIs were performed at baseline, Month 6, and Month 12. In the 2-year RADIANCE study, brain MRIs were performed at baseline, Month 12, and Month 24.[2,3]

9 of 10 Patients Showed No Confirmed 3-Month Disability Progression[1]

SECONDARY ENDPOINT — **Confirmed Disability Progression at 2 Years** — **POOLED ANALYSIS**

92.4% vs **92.2% for Avonex** Showed **No Confirmed** 3-Month **Disability Progression**



Statistical significance was not reached for the pooled CDP.

7.6% of patients treated with ZEPOSIA (n=67/880) experienced 3-month confirmed disability progression (CDP), as measured by EDSS, similar to Avonex (7.8%; n=69/889) (*P*=NS)[1,3]

CDP was defined as at least a 1-point increase from baseline EDSS confirmed after 3 months and after 6 months. CDP was prospectively evaluated in a pooled analysis from the SUNBEAM and RADIANCE studies.

EDSS=Expanded Disability Status Score; NS=nonsignificant.

IMPORTANT SAFETY INFORMATION (CONTINUED)

Bradyarrhythmia and Atrioventricular Conduction Delays: Since initiation of ZEPOSIA may result in a transient decrease in heart rate and atrioventricular conduction delays, dose titration is recommended to help reduce cardiac effects. Initiation of ZEPOSIA without dose escalation may result in greater decreases in heart rate. If treatment with ZEPOSIA is considered, advice from a cardiologist should be sought for those individuals:

- with significant QT prolongation
- with arrhythmias requiring treatment with Class 1a or III anti-arrhythmic drugs
- with ischemic heart disease, heart failure, history of cardiac arrest or myocardial infarction, cerebrovascular disease, and uncontrolled hypertension
- with a history of Mobitz type II second-degree or higher AV block, sick-sinus syndrome, or sinoatrial heart block

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Compelling Efficacy in Brain Volume Loss Data in Pivotal Trials[2,3]

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SECONDARY ENDPOINT — **Whole Brain Volume Loss**

Mean Percent Change From Baseline

SUNBEAM (1 Year)

31% RELATIVE REDUCTION

ZEPOSIA: –0.41 (n=397)

vs Avonex: –0.61 (n=406)

RADIANCE (2 Years)

26% RELATIVE REDUCTION

ZEPOSIA: –0.71 (n=390)

vs Avonex: –0.94 (n=397)

EXPLORATORY ENDPOINT — **Thalamic Volume Loss**

Mean Percent Change From Baseline

SUNBEAM (1 Year)

32% RELATIVE REDUCTION

ZEPOSIA: –1.12 (n=393)

vs Avonex: –1.72 (n=406)

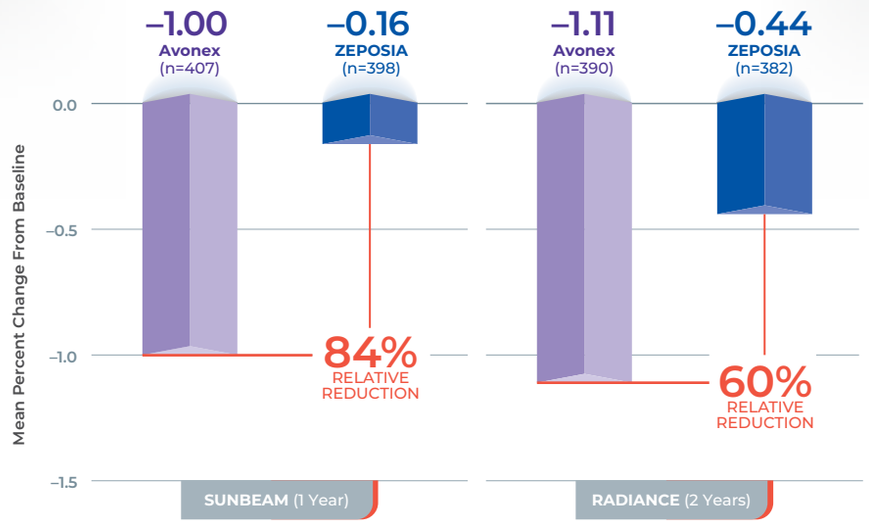
RADIANCE (2 Years)

27% RELATIVE REDUCTION

ZEPOSIA: –1.40 (n=385)

vs Avonex: –1.85 (n=391)

EXPLORATORY ENDPOINT — **Cortical Grey Matter Volume Loss**



Volume loss endpoints were not part of the statistical analysis hierarchy.

View **RADIANCE Age-Based Breakouts**

In the 1-year SUNBEAM study, brain MRIs were performed at baseline, Month 6, and Month 12.[2]
In the 2-year RADIANCE study, brain MRIs were performed at baseline, Month 12, and Month 24.[3]

IMPORTANT SAFETY INFORMATION (CONTINUED)

Liver Injury: Elevations of aminotransferases may occur in patients receiving ZEPOSIA. Obtain liver function tests, if not recently available (i.e., within 6 months), before initiation of ZEPOSIA. Patients who develop symptoms suggestive of hepatic dysfunction should have hepatic enzymes checked and ZEPOSIA should be discontinued if significant liver injury is confirmed. Caution should be exercised when using ZEPOSIA in patients with history of significant liver disease

Fetal Risk: There are no adequate and well-controlled studies in pregnant women. Based on animal studies, ZEPOSIA may cause fetal harm. Women of childbearing potential should use effective contraception to avoid pregnancy during treatment and for 3 months after stopping ZEPOSIA

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Post Hoc Analysis: SDMT—Cognitive Processing Speed Data (SUNBEAM and OLE)[14,15]

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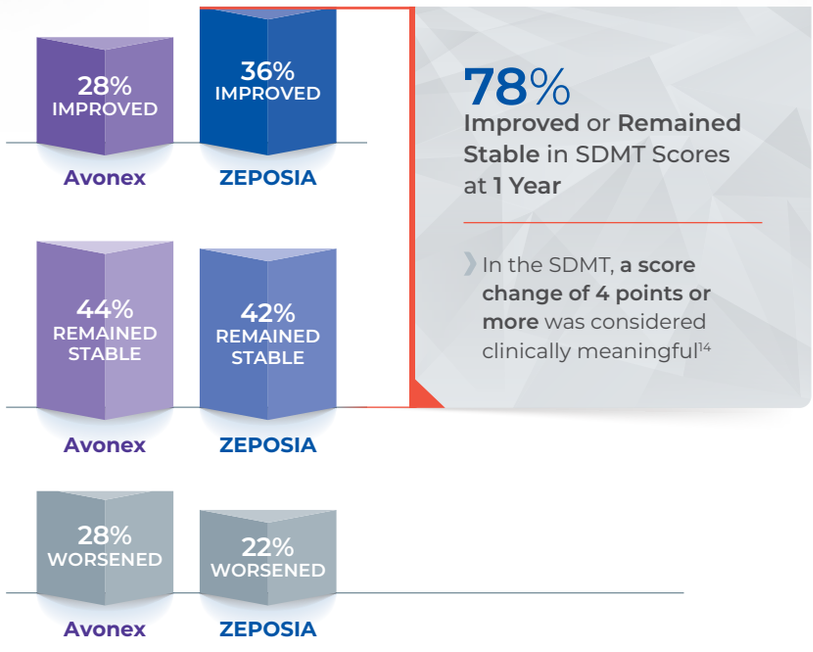
POST HOC **ANALYSIS** **SDMT Scores From SUNBEAM** (1 Year)[14]



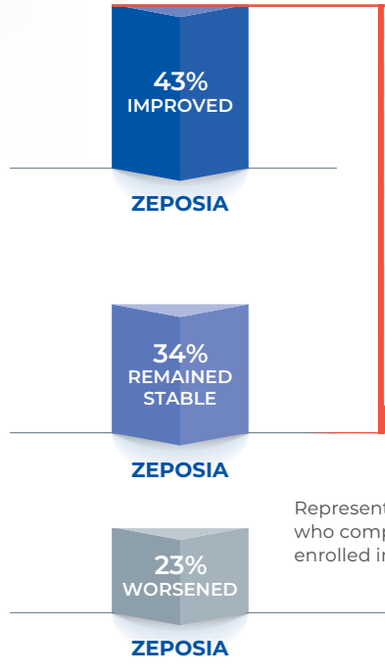
78%
Improved or **Remained Stable** in SDMT Scores at **1 Year**

In the SDMT, **a score change of 4 points or more** was considered clinically meaningful[14]

ZEPOSIA: n=427 at Month 12 for SDMT; Avonex: n=426 at Month 12 for SDMT

POST HOC **ANALYSIS** **SDMT Scores From DAYBREAK** (OLE)[15]

Categorical Analysis of Clinically Meaningful Change in SDMT Relative to SUNBEAM Baseline[a]



77%
Improved or **Remained Stable** in SDMT Scores at **Month 42**

In the SDMT, **a score change of ≥4 points or ≥10%** is considered clinically meaningful[15]

Represents participants receiving ZEPOSIA 0.92 mg who completed the SUNBEAM phase 3 trial and enrolled in the open-label extension study.

ZEPOSIA: n=376 at Month 42 for SDMT

This endpoint was not part of the statistical analysis hierarchy for SUNBEAM and was analyzed descriptively in DAYBREAK.

The MSFC was a secondary endpoint made up of 3 components: 9-hole peg test (arm/hand function), timed 25-foot walk (ambulation), and SDMT (cognitive function).[2,14,16]

SDMT is a tool that measures cognitive processing speed.[17]

[a]Data cutoff for this interim analysis was December 20, 2019.

MSFC=Multiple Sclerosis Functional Composite.

IMPORTANT SAFETY INFORMATION (CONTINUED)

Increased Blood Pressure: Increase in systolic pressure was observed after about 3 months of treatment and persisted throughout treatment. Blood pressure should be monitored during treatment and managed appropriately. Certain foods that may contain very high amounts of tyramine could cause severe hypertension in patients taking ZEPOSIA. Patients should be advised to avoid foods containing a very large amount of tyramine while taking ZEPOSIA

Respiratory Effects: ZEPOSIA may cause a decline in pulmonary function. Spirometric evaluation of respiratory function should be performed during therapy, if clinically indicated

Please see Important Safety Information throughout and full Prescribing Information and Medication Guide.

Safety Profile Comparable to Avonex in Overall Incidence of Adverse Reactions,[2,3] With Generally Similar Safety Demonstrated in the Ongoing, Open-Label Extension Study[13]

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	SUNBEAM		RADIANCE	
	Avonex n=445	ZEPOSIA n=448	Avonex n=440	ZEPOSIA n=434
Overall incidence of adverse reactions	75.5%	59.8%	83.0%	74.7%
Severe adverse reactions	2.2%	1.6%	4.3%	3.5%
Serious adverse reactions	2.5%	2.9%	6.4%	6.5%

Adverse Reactions With an Incidence of at Least 2% in Patients Treated With ZEPOSIA and at Least 1% Greater Than Avonex[1a]

SUNBEAM AND RADIANCE: POOLED DATA

Adverse Reactions	Avonex n=885	ZEPOSIA n=882
Upper respiratory infection[b]	23%	26%
Hepatic transaminase elevation[c]	5%	10%
Orthostatic hypotension	3%	4%
Urinary tract infection	3%	4%
Back pain	3%	4%
Hypertension[d]	2%	4%
Abdominal pain upper	1%	2%

Adverse reactions are sorted by decreasing incidence in patients treated with ZEPOSIA. For adverse reactions pertaining to liver function tests, increases were transient and generally resolved without discontinuation.[1] Elevations of 3-fold the ULN or greater occurred in 5.5% of patients taking ZEPOSIA and in 3.1% of patients taking Avonex. The majority (79%) continued treatment with ZEPOSIA with values returning to less than 3 times the ULN within approximately 2 to 4 weeks.[1]

Data Up to 3-Years[e]: Summary of TEAEs in DAYBREAK in Patients Treated With ZEPOSIA[13]

PRIMARY ENDPOINT DAYBREAK OLE

	ZEPOSIA n=846
Any TEAE	80.6%
Severe TEAEs	4.6%
Serious TEAEs	9.5%
TEAEs leading to permanent treatment discontinuation	1.7%

TEAEs in ≥4% of patients treated with ZEPOSIA	ZEPOSIA n=846
Nasopharyngitis	17.1%
Headache	14.1%
Upper respiratory tract infection	9.5%
Lymphopenia	8.2%
ALC decreased	8.2%
Back pain	6.6%
Urinary tract infection	5.0%
GGT increased	4.7%
Hypertension	4.3%

TEAEs are sorted by decreasing incidence in patients treated with ZEPOSIA

[a]Data are not an adequate basis for comparison of rates between ZEPOSIA and the active control.
[b]Includes the following terms: nasopharyngitis, upper respiratory tract infection, pharyngitis, respiratory tract infection, bronchitis, rhinitis, respiratory tract infection viral, viral upper respiratory tract infection, rhinorrhea, tracheitis, and laryngitis.
[c]Includes the following terms: alanine aminotransferase increased, gamma-glutamyl transferase increased, aspartate aminotransferase increased, hepatic enzyme increased, liver function test abnormal, and transaminases increased.
[d]Includes hypertension, essential hypertension, and orthostatic hypertension.
[e]Study period includes DAYBREAK Day 1 through last treatment date or the data-cutoff date.
AE=adverse event; ALC=absolute lymphocyte count; GGT=gamma-glutamyl transferase; S1P=sphingosine-1-phosphate; TEAE=treatment-emergent adverse event; ULN=upper limit of normal.

IMPORTANT SAFETY INFORMATION (CONTINUED)

Macular edema: S1P modulators have been associated with an increased risk of macular edema. Patients with a history of uveitis or diabetes mellitus are at increased risk. Patients with a history of these conditions should have an ophthalmic evaluation of the fundus, including the macula, prior to treatment initiation and regular follow-up examinations. An ophthalmic evaluation is recommended in all patients at any time if there is a change in vision. Continued use of ZEPOSIA in patients with macular edema has not been evaluated; potential benefits and risks for the individual patient should be considered if deciding whether ZEPOSIA should be discontinued

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≥90% of Patients Treated With ZEPOSIA Stayed on Therapy Through Completion of Pivotal Trials[1]

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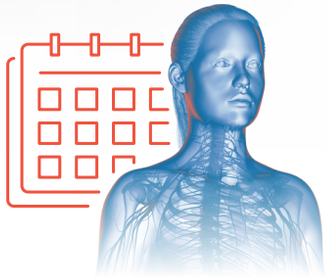
≥90% of Patients Stayed on Therapy Through Completion of Pivotal Trials



SUNBEAM (1 Year)

94% Remained on ZEPOSIA at **1 Year** and **92%** Remained on Avonex[1]

RADIANCE (2 Years)

90% Remained on ZEPOSIA at **2 Years** and **85%** Remained on Avonex[1]

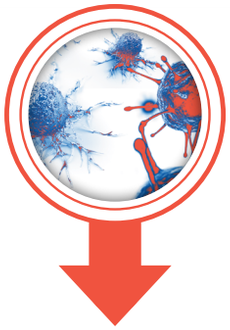
Low discontinuation rates due to AEs[2,3]

SUNBEAM (1 Year)

2.9% for ZEPOSIA and **3.6%** for Avonex[2]

RADIANCE (2 Years)

3.0% for ZEPOSIA and **4.1%** for Avonex[3]



Rates of Serious Infections and Malignancies Consistent vs Avonex[1]

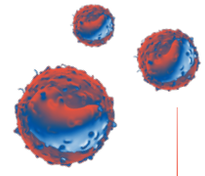
The rate of serious infections at 1 year for ZEPOSIA was 1.1% vs 0.7% for Avonex and the rate at 2 years for ZEPOSIA was 0.9% vs 0.9% for Avonex. The rate of malignancies at 1 year for ZEPOSIA was 0.2% vs 0% for Avonex and the rate at 2 years for ZEPOSIA was 0.9% vs 0.5% for Avonex.[2,3]

Overall Infections

In SUNBEAM and RADIANCE, the overall rate of infections with ZEPOSIA (35%) was similar to Avonex (34%).[1] ZEPOSIA causes a reduction in peripheral blood lymphocyte count and may increase the risk of infection[1]

Controlled Lymphocyte Reductions

ALC was consistently maintained near the lower limit of normal across both pivotal trials, and the mean ALC for both SUNBEAM and RADIANCE was **≈0.8 × 10^9/L**.[2,3,18]



View **ALC Data**

Herpetic Infections: In active-controlled MS trials, herpes zoster was reported as an adverse reaction in 0.6% of patients treated with ZEPOSIA 0.92 mg and in 0.2% of patients taking Avonex.[1]

IMPORTANT SAFETY INFORMATION (CONTINUED)

Posterior Reversible Encephalopathy Syndrome (PRES): Rare cases of PRES have been reported in patients receiving a S1P receptor modulator. If a ZEPOSIA-treated patient develops unexpected neurological or psychiatric symptoms or any symptom/sign suggestive of an increase in intracranial pressure, a complete physical and neurological examination should be conducted. Symptoms of PRES are usually reversible but may evolve into ischemic stroke or cerebral hemorrhage. Delay in diagnosis and treatment may lead to permanent neurological sequelae. If PRES is suspected, treatment with ZEPOSIA should be discontinued

Please see Important Safety Information throughout and full Prescribing Information and Medication Guide.

Getting Started on ZEPOSIA[1]

once-daily ZEPOSIA® (ozanimod) 0.92 mg capsules

ZEPOSIA 7-Day Titration Schedule

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8+
ZEPOSIA	0.23 mg once daily				0.46 mg once daily			0.92 mg once daily

One Capsule, Once a Day, From the Start[1]

An up-titration schedule should be used to reach the maintenance dose, as a transient decrease in heart rate and AV conduction delays may occur[1]

Full Prescribing Information for ZEPOSIA Has

NO Genetic Testing

NO Ophthalmic Testing for Most Patients[1,19a]

NO First-Dose Observation Required

Minimal Pre-Initiation Requirements

Before Initiating Treatment With ZEPOSIA...

- Obtain a **CBC** (within 6 months or after discontinuation of prior MS therapy), including lymphocyte count
- Obtain an **ECG** to determine whether preexisting conduction abnormalities are present
- Obtain **transaminase and bilirubin levels** (within 6 months)
- Evaluate **current and prior medications**
- Patients without a confirmed history of VZV or without documented VZV vaccination should be tested for antibodies. If VZV or other live attenuated **immunizations are required**, administer at least 1 month prior to initiation

[a]Diabetes mellitus and uveitis increase the risk of macular edema; patients with a history of these conditions should have an ophthalmic evaluation of the fundus, including the macula, prior to treatment initiation. A prompt ophthalmic evaluation is recommended if there is any change in vision while taking ZEPOSIA.

AV=atrioventricular; CBC=complete blood count; ECG=electrocardiogram; VZV=varicella-zoster virus.

IMPORTANT SAFETY INFORMATION (CONTINUED)

Immune System Effects After Stopping ZEPOSIA: After discontinuing ZEPOSIA, the median time for lymphocyte counts to return to the normal range was 30 days with approximately 90% of patients in the normal range within 3 months. Use of immunosuppressants within this period may lead to an additive effect on the immune system, therefore caution should be applied when initiating other drugs 4 weeks after the last dose of ZEPOSIA

Most common Adverse Reactions (≥ 4%): upper respiratory infection, hepatic transaminase elevation, orthostatic hypotension, urinary tract infection, back pain, and hypertension.

Please see Important Safety Information throughout and full Prescribing Information and Medication Guide.

ZEPOSIA—FOCUSED ON WHAT COUNTS

once-daily ZEPOSIA® (ozanimod) 0.92 mg capsules

START AS SOON AS TODAY

COMPELLING ARR EFFICACY[1a]

Absolute ARR:

SUNBEAM (1 Year): **0.18**[1]
RADIANCE (2 Years): **0.17**[1]
DAYBREAK (Up to 3 Years[b], OLE): **0.11**[1,3]

BRAIN VOLUME DATA

Brain Volume: Whole brain and grey matter volume loss vs Avonex[2,3]

SAFETY PROFILE COMPARABLE TO AVONEX IN OVERALL INCIDENCE OF ADVERSE REACTIONS[2,3c]

≥90% of PATIENTS treated with ZEPOSIA stayed on therapy Through Completion of Pivotal Trials[1d]

ONE CAPSULE, ONCE A DAY, RIGHT FROM THE START[1]

Minimal pre-initiation assessments[e]

[a]**Study designs:** SUNBEAM (1 year; N=1346) and RADIANCE (2 years; N=1313) were multicenter, randomized, double-blind, double-dummy, active treatment-controlled studies of daily oral ozanimod 0.46 mg (not approved for maintenance dose) or 0.92 mg vs weekly Avonex (interferon beta-1a), 30-µg intramuscular injection. **Primary endpoint:** ZEPOSIA reduced ARR vs Avonex by 48% at 1 year (0.18 vs 0.35, respectively) and by 38% at 2 years (0.17 vs 0.28, respectively). **Secondary endpoints:** ZEPOSIA reduced the number of new or enlarging T2 lesions by 48% at 1 year and by 42% at 2 years and reduced the number of GdE lesions vs Avonex by 63% at 1 year and 53% at 2 years. 9 of 10 patients showed no confirmed 3-month disability progression. There was no significant difference in 3-month confirmed disability between ZEPOSIA and Avonex.[1-3]

[b]Study period includes DAYBREAK Day 1 through last treatment date or the data-cutoff date.

[c]**Adverse reactions:** Overall incidence of adverse reactions for ZEPOSIA vs Avonex at 1 year was 59.8% and 75.5%, respectively, and at 2 years was 74.7% and 83.0%, respectively. Across 2 head-to-head trials, the most common adverse reactions with an incidence of at least 2% in patients treated with ZEPOSIA and at least 1% greater than Avonex, respectively, were as follows: upper respiratory infection, 26% (vs 23%); hepatic transaminase elevation, 10% (vs 5%); orthostatic hypotension, 4% (vs 3%); urinary tract infection, 4% (vs 3%); back pain, 4% (vs 3%); hypertension, 4% (vs 2%); and abdominal pain upper, 2% (vs 1%). Data are not an adequate basis for comparison of rates between ZEPOSIA and the active control. Upper respiratory infection includes nasopharyngitis, upper respiratory tract infection, pharyngitis, respiratory tract infection, bronchitis, rhinitis, respiratory tract infection viral, viral upper respiratory tract infection, rhinorrhea, tracheitis, and laryngitis. Hepatic transaminase elevation includes alanine aminotransferase increased, gamma-glutamyl transferase increased, aspartate aminotransferase increased, hepatic enzyme increased, liver function test abnormal, and transaminase increased. Hypertension includes hypertension, essential hypertension, and orthostatic hypertension. Overall discontinuation rates for ZEPOSIA vs Avonex at 1 year were 6% and 8%, respectively, and at 2 years were 10% and 15%, respectively. Discontinuation rates due to adverse reactions for ZEPOSIA vs Avonex at 1 year were 2.9% and 3.6%, respectively, and at 2 years were 3.0% and 4.1%, respectively. **Serious infections:** The rate of serious infections at 1 year for ZEPOSIA was 1.1% vs 0.7% for Avonex and the rate at 2 years for ZEPOSIA was 0.9% vs 0.9% for Avonex. **Malignancy rates:** The rate of malignancies at 1 year for ZEPOSIA was 0.2% vs 0% for Avonex and the rate at 2 years for ZEPOSIA was 0.9% vs 0.5% for Avonex.[1-3]

[d]In the 1-year SUNBEAM trial, 94% of patients who received ZEPOSIA (n=447) and 92% who received Avonex (n=448) completed the study. In the 2-year RADIANCE trial, 90% of patients who received ZEPOSIA (n=433) and 85% who received Avonex (n=441) completed the study.

[e]Before initiating treatment with ZEPOSIA, all patients require a recent CBC including lymphocyte count (within 6 months or after discontinuation of prior MS therapy), an ECG to check for preexisting conduction abnormalities, a recent liver function test (within 6 months), and consideration of current and prior medications, including vaccinations.[1] Patients without a confirmed history of varicella (chickenpox) or without documented VZV vaccination should be tested for antibodies. If VZV or other live attenuated immunizations are required, administer at least 1 month prior to initiation.[1] For patients with a history of uveitis or macular edema, an ophthalmic assessment is required.1 An up-titration scheme should be used to reach the maintenance dosage of ZEPOSIA, as a transient decrease in heart rate and atrioventricular conduction delays may occur.[1]

Indication

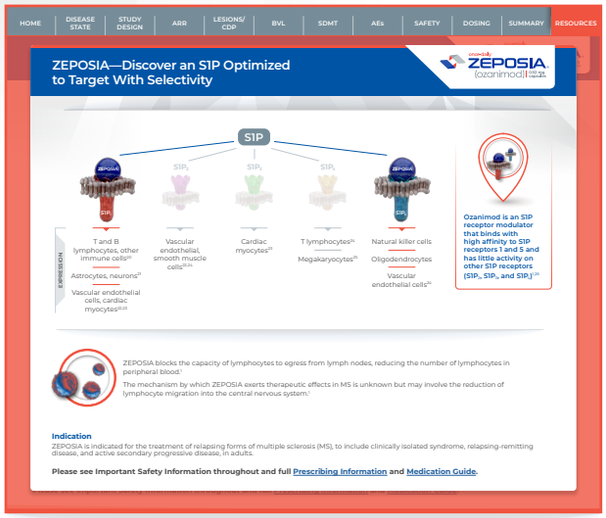
ZEPOSIA is indicated for the treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults.

Please see Important Safety Information throughout and full Prescribing Information and Medication Guide.

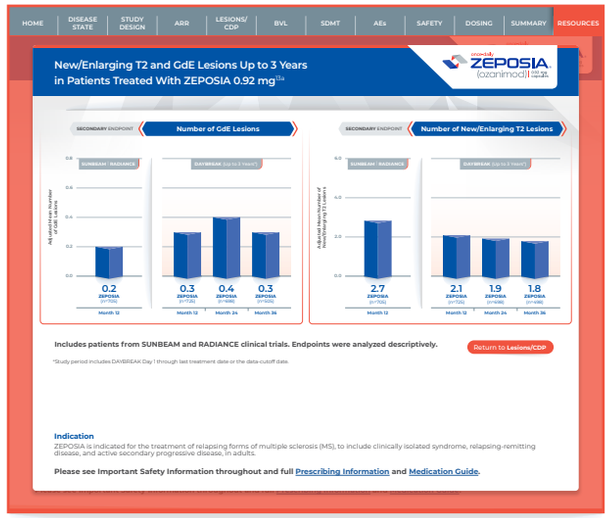
Bristol Myers Squibb™

Resources

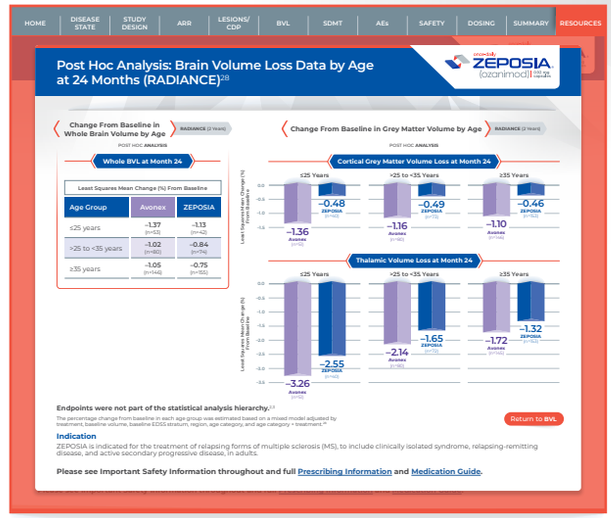
once-daily ZEPOSIA® (ozanimod) 0.92 mg capsules



MOA

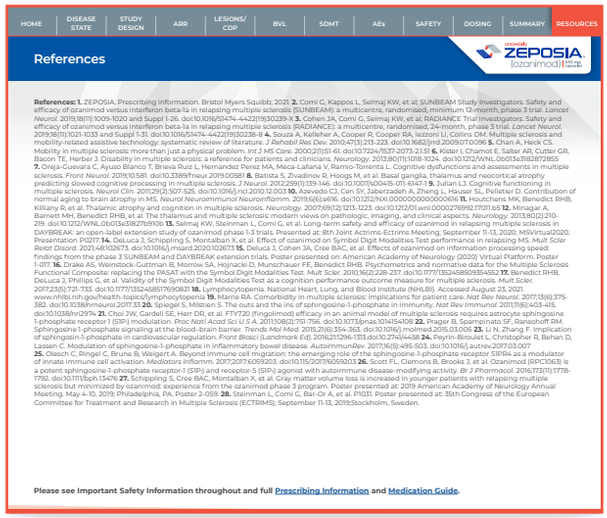


LESIONS/OLE



BVL—AGE-BASED

ALC

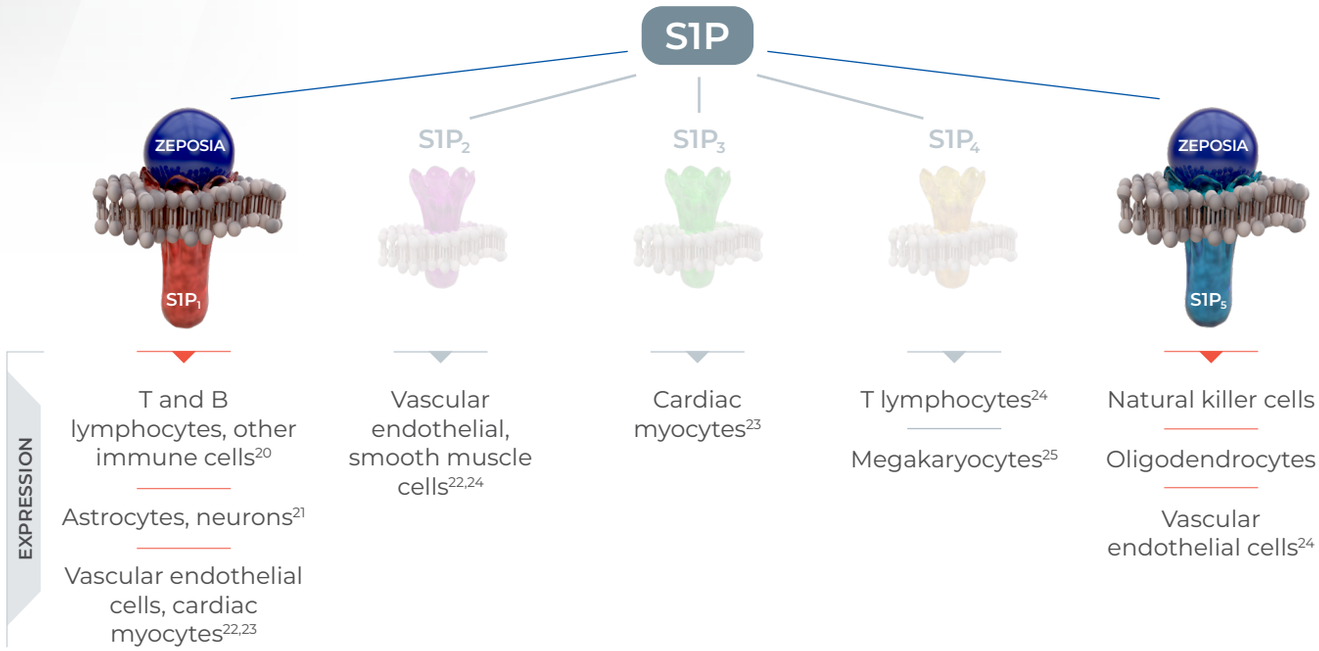


REFERENCES

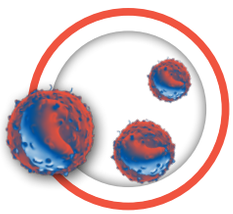
Please see Important Safety Information throughout and full Prescribing Information and Medication Guide.

ZEPOSIA—Discover an S1P Optimized to Target With Selectivity

once-daily ZEPOSIA® (ozanimod) | 0.92 mg capsules



Ozanimod is an S1P receptor modulator that binds with high affinity to S1P receptors 1 and 5 and has little activity on other S1P receptors ($S1P_2$, $S1P_3$, and $S1P_4$)[1,26]



ZEPOSIA blocks the capacity of lymphocytes to egress from lymph nodes, reducing the number of lymphocytes in peripheral blood.[1]

The mechanism by which ZEPOSIA exerts therapeutic effects in MS is unknown but may involve the reduction of lymphocyte migration into the central nervous system.[1]

Indication

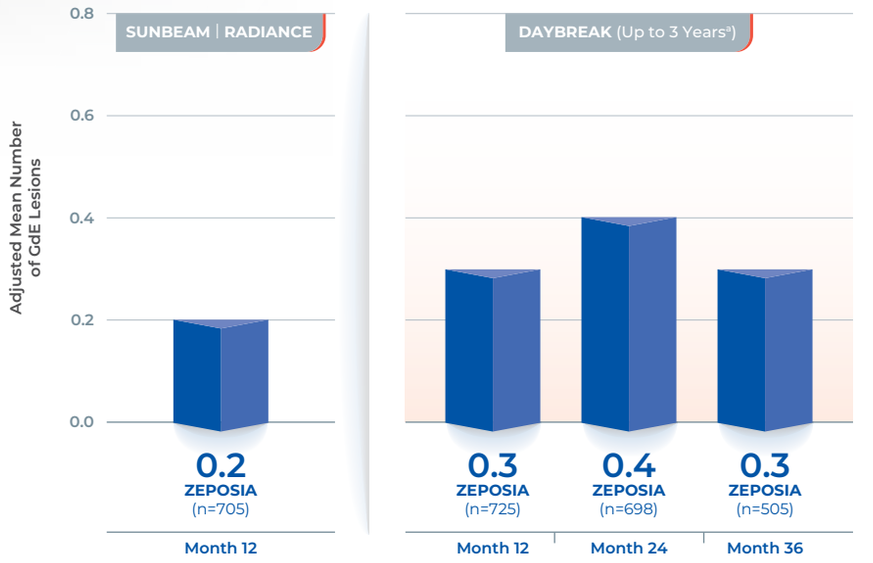
ZEPOSIA is indicated for the treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults.

Please see Important Safety Information throughout and full Prescribing Information and Medication Guide.

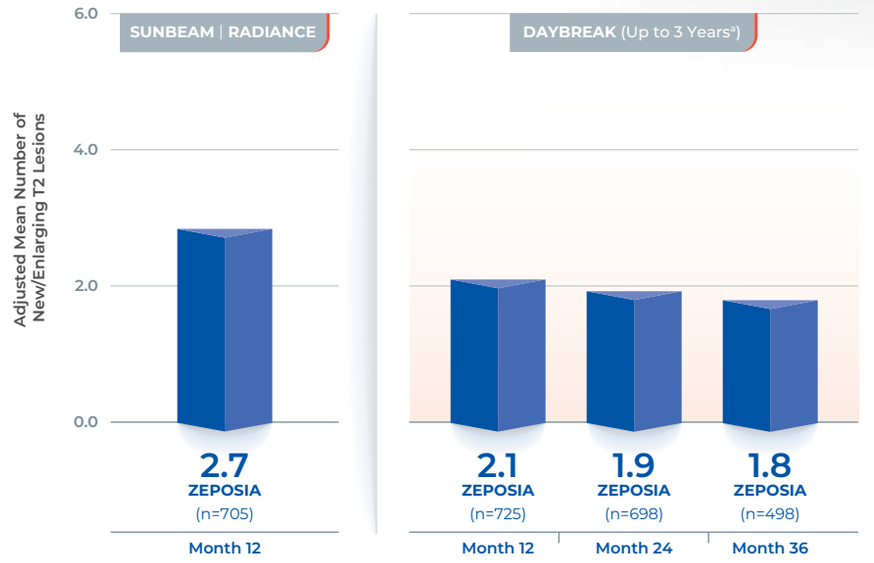
New/Enlarging T2 and GdE Lesions Up to 3 Years in Patients Treated With ZEPOSIA 0.92 mg[13a]

once-daily ZEPOSIA (ozanimod) | 0.92 mg capsules

SECONDARY ENDPOINT — **Number of GdE Lesions**



SECONDARY ENDPOINT — **Number of New/Enlarging T2 Lesions**



Includes patients from SUNBEAM and RADIANCE clinical trials. Endpoints were analyzed descriptively.

Return to **Lesions/CDP**

[a]Study period includes DAYBREAK Day 1 through last treatment date or the data-cutoff date.

Indication

ZEPOSIA is indicated for the treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults.

Please see Important Safety Information throughout and full Prescribing Information and Medication Guide.

Post Hoc Analysis: Brain Volume Loss Data by Age at 24 Months (RADIANCE)[28]

once-daily ZEPOSIA® (ozanimod) | 0.92 mg capsules

Change From Baseline in Whole Brain Volume by Age

RADIANCE (2 Years)

POST HOC **ANALYSIS**

Whole BVL at Month 24

Least Squares Mean Change (%) From Baseline

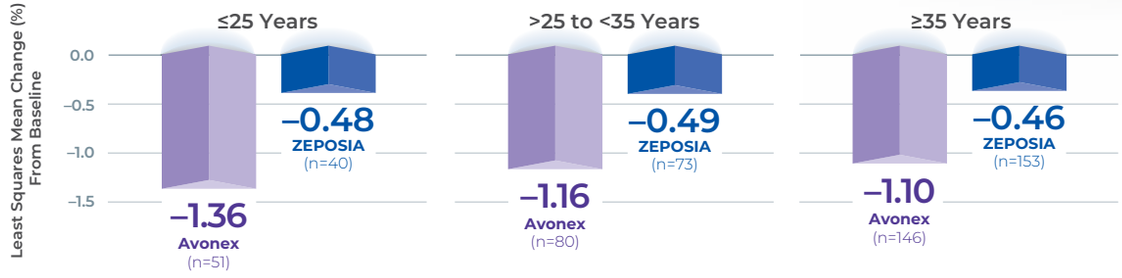
Age Group	Avonex	ZEPOSIA
≤25 years	–1.37 (n=53)	–1.13 (n=42)
>25 to <35 years	–1.02 (n=80)	–0.84 (n=74)
≥35 years	–1.05 (n=146)	–0.75 (n=155)

Change From Baseline in Grey Matter Volume by Age

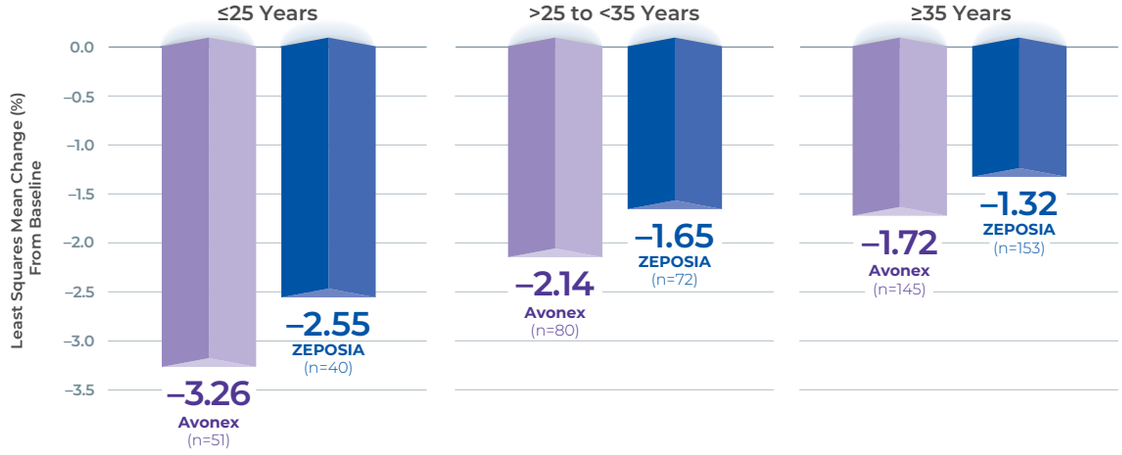
RADIANCE (2 Years)

POST HOC **ANALYSIS**

Cortical Grey Matter Volume Loss at Month 24



Thalamic Volume Loss at Month 24



Endpoints were not part of the statistical analysis hierarchy.[2,3]

The percentage change from baseline in each age group was estimated based on a mixed model adjusted by treatment, baseline volume, baseline EDSS stratum, region, age category, and age category × treatment.[28]

Return to **BVL**

Indication

ZEPOSIA is indicated for the treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults.

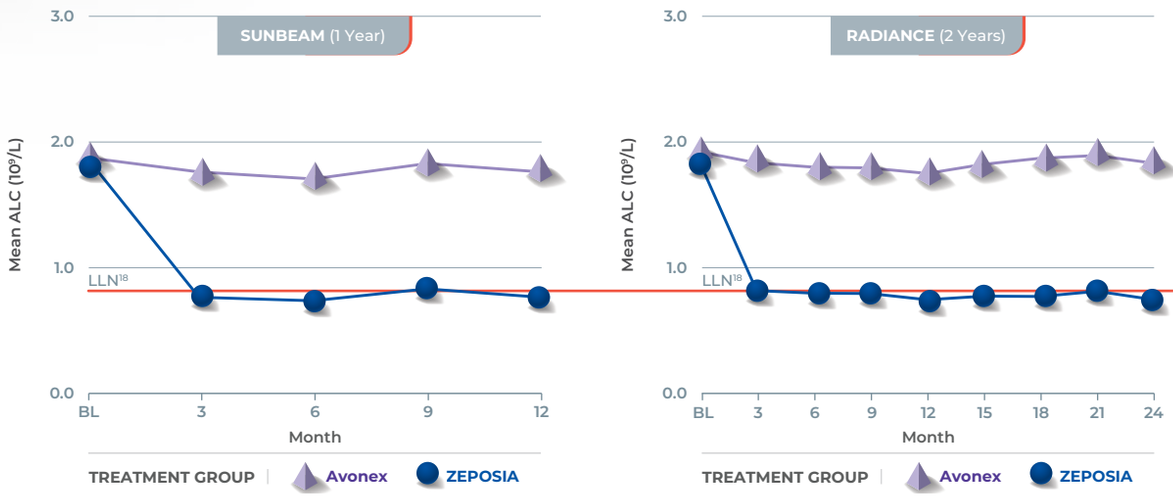
Please see Important Safety Information throughout and full Prescribing Information and Medication Guide.

ZEPOSIA Consistently Maintained ALC Near the Lower Limit of Normal[2,3]

once-daily ZEPOSIA® (ozanimod) | 0.92 mg capsules

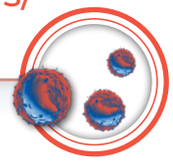
Mean ALC

Consistently Maintained Near the LLN at a **Mean Lymphocyte Count of ≈0.8 × 10⁹/L**



Maintained Near the LLN at a Mean Lymphocyte Count of

≈800 lymphocytes/ µL of blood



Lymphocyte numbers can be restored to normal values by discontinuing therapy[1-3,28]

- **After discontinuing** ZEPOSIA 0.92 mg, the median time for peripheral blood lymphocytes to return to the normal range was 30 days, with approximately 90% of patients in the normal range within 3 months
- **Mean ALC was approximately 0.8 × 10⁹ cells/L** for both SUNBEAM and RADIANCE (at 1 year and 2 years, respectively)
- **ZEPOSIA causes a mean reduction** in peripheral blood lymphocyte count to approximately 45% of baseline values because of reversible sequestration of lymphocytes in lymphoid tissues; ZEPOSIA may therefore increase the susceptibility to infections, some serious in nature
- **During clinical trials**, a combined total of 29 patients treated with ZEPOSIA 0.92 mg from SUNBEAM and RADIANCE had an ALC of <200 cells/µL. If ALC counts <200 cells/µL were found and confirmed on repeat testing, treatment was temporarily stopped until lymphocyte counts reached >500 cells/µL

BL=baseline; LLN=lower limit of normal.

Indication

ZEPOSIA is indicated for the treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults.

Please see Important Safety Information throughout and full Prescribing Information and Medication Guide.

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