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Concurrent administration of serotonergic antidepressants and ozanimod in participants with relapsing multiple sclerosis from the open-label extension DAYBREAK trial

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Abstract

Background: Monoamine oxidase (MAO) inhibitors can interact with selective serotonin reuptake inhibitors (SSRIs)/serotonin–norepinephrine reuptake inhibitors (SNRIs). There is clinical interest surrounding use of ozanimod with SSRIs/SNRIs because the major metabolites of ozanimod are weak inhibitors of MAO-B in vitro.

Objective: To evaluate the incidence of treatment-emergent adverse events (TEAEs) potentially related to serotonin accumulation (SA) during concomitant ozanimod and SSRI/SNRI use by performing analyses of data from an open-label, oral ozanimod 0.92 mg trial (DAYBREAK; NCT02576717).

Methods: SA narrow (serotonin syndrome, neuroleptic malignant syndrome, and hyperthermia malignant) and broad (terms potentially associated with SA) MedDRA v24.0 searches were performed using TEAE data from participants with relapsing multiple sclerosis who entered DAYBREAK from phase 3 studies (cutoff February 1, 2022). Incidences of TEAEs matching terms from each search were stratified by SSRI/SNRI use.

Results: Of 2257 DAYBREAK participants, 274 (12.1%) used an SSRI/SNRI. No participants had TEAEs matching the SA narrow search terms. There was no significant difference in the percentage of participants with ≥ 1 TEAE matching the SA broad search for those on versus off SSRIs/SNRIs (on: 12.4%, $n=34/274$; off: 15.6%, $n=310/1982$, nominal $p=0.1630$).

Conclusion: MedDRA searches showed no increase in TEAEs potentially associated with SA with concomitant SSRI/SNRI and ozanimod use.

Keywords: Multiple sclerosis, sphingosine 1-phosphate receptor modulators, selective serotonin reuptake inhibitors, serotonin–norepinephrine reuptake inhibitors

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Introduction

Depression and anxiety are prevalent comorbidities occurring in up to 54% of people with multiple sclerosis (MS)¹; thus, patients with MS may receive selective serotonin reuptake inhibitors (SSRIs) or serotonin–norepinephrine reuptake inhibitors (SNRIs) as a first-line treatment for major depressive and generalized anxiety disorders.^{2,3} Although SSRIs and SNRIs are generally well tolerated, there are potential drug–drug

interactions, particularly when other serotonergic agents are used concomitantly.^{4,5} For example, serotonin accumulation (SA) may occur when SSRIs/SNRIs are used in combination with tramadol, high-dose triptans, or linezolid through the inhibition of monoamine oxidase (MAO).⁵ Of the drugs that inhibit MAO, SA is more likely with MAO-A inhibition than MOA-B inhibition because MAO-A is more involved in serotonin breakdown than MAO-B.⁶



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Ozanimod is a sphingosine 1-phosphate (S1P) receptor 1 and 5 modulator approved in multiple countries for the treatment of adults with relapsing forms of MS (RMS) or moderately to severely active ulcerative colitis.^{7,8} One major active metabolite of ozanimod, CC112273, is a substrate of MAO-B, and both major active metabolites (CC112273 and CC1084037) are weak inhibitors of MAO-B, but not MAO-A, *in vitro*.^{9,10} In a multiple-dose pharmacokinetic study, ozanimod treatment did not lead to the inhibition of human platelet MAO-B activity *in vivo*.¹⁰ Considering MAO-B inhibition reduces the deamination of norepinephrine, leading to a hypothetically enhanced pressor effect of pseudoephedrine, the potential pharmacokinetic interactions of ozanimod and pseudoephedrine were also assessed in healthy participants.¹⁰ Steady-state exposure to the major active metabolites of ozanimod did not potentiate the effect of pseudoephedrine on blood pressure, further supporting the lack of inhibitory effects on MAO-B in humans.¹⁰ A statement in the April 2023 version of the ozanimod prescribing information describes the potential for serious adverse reactions, including hypertensive crisis, during coadministration of ozanimod with drugs that increase serotonin or norepinephrine such as SSRIs and SNRIs.⁸

To address the concern identified from other MAO-A and MAO-B inhibitors that concomitant use with SSRIs/SNRIs could lead to SA, this analysis was conducted to evaluate the incidence of treatment-emergent adverse events (TEAEs) that could be related to SA during concomitant SSRI/SNRI use in ozanimod-treated participants with RMS from the DAYBREAK open-label extension (OLE) trial.

Methods

Study design

This analysis included participants with RMS who entered DAYBREAK (NCT02576717) from two phase 3 trials (SUNBEAM (NCT02294058; duration: ≥ 12 months) and RADIANCE (NCT02047734; duration: 24 months)). RADIANCE¹¹ and SUNBEAM¹² were multicenter, randomized, double-blind, double-dummy, active-controlled, phase 3 trials that assessed the efficacy and safety of ozanimod in participants with RMS. Participants who completed these trials were eligible to enroll in the ongoing, single-arm, multicenter, OLE DAYBREAK trial, aimed to characterize the long-term safety and efficacy of ozanimod

0.92 mg in RMS.¹³ The DAYBREAK study began on 16 October 2015,¹³ and data here were generated using a 1 February 2022 cutoff. Participants in SUNBEAM, RADIANCE, and DAYBREAK were allowed concurrent SSRI/SNRI use. In this analysis, participants from SUNBEAM or RADIANCE who were taking SSRIs/SNRIs in DAYBREAK were compared with those who did not take an SSRI/SNRI concomitantly. Although formally a serotonin antagonist and reuptake inhibitor, trazodone was also included because it may also cause SA¹⁴ and was commonly used by participants enrolled in DAYBREAK.

The institutional review board or ethics committee at each site approved the protocols of the RADIANCE¹¹ and SUNBEAM¹² trials, which conformed to Good Clinical Practice guidelines and Declaration of Helsinki principles. All participants who entered DAYBREAK consented by written agreement before entering the OLE trial.¹³

Study procedures and outcomes

A primary SA narrow Medical Dictionary for Regulatory Activities (MedDRA (version 24.0)) search was conducted using TEAE data from DAYBREAK with the following preferred terms: serotonin syndrome, neuroleptic malignant syndrome, and hyperthermia malignant. This search was supplemented with a secondary, broader SA MedDRA search based on a standardized MedDRA query for neuroleptic malignant syndrome (substantial overlap of potential symptoms with SA) that was supplemented with SA-specific terms (see Supplemental Table 1 for all search terms used in this analysis). Hypertension was included in the SA broad search terms as a key manifestation of neuroleptic malignant syndrome and the potential autonomic hyperactivity that can accompany increased serotonin levels, while also being a known effect of S1P receptor modulators via impaired endothelial-dependent vasodilation.^{15–17} Participants were counted at most once per system organ class or preferred term for multiple occurrences.

A TEAE was defined as an adverse event with a start date on or after the date of the first dose of ozanimod in DAYBREAK. A participant was categorized as on an SSRI/SNRI for a TEAE preferred term if ≥ 1 TEAE occurred while taking an SNRI/SSRI. A participant was counted as not on an SSRI/SNRI for a TEAE preferred term if they did not receive an SSRI/SNRI in DAYBREAK.

Statistical analysis

Duration of exposure to SSRIs/SNRIs was defined as the period when participants were exposed to ≥ 1 SSRI/SNRI and ozanimod during the analysis period.

The percentage of participants who had ≥ 1 TEAE matching the terms from each MedDRA search was determined and stratified by SSRI/SNRI use and compared using a chi-square test. All statistical comparisons are considered as hypothesis generating rather than declarative, and *p*-values are nominal. Incidences of TEAEs from individual terms from the SA broad search were also stratified by SSRI/SNRI use and captured >1 day from the start date of concomitant treatment with ozanimod (broad window). To assess whether potential SA-related TEAEs were clustered around the start of concomitant use of an SSRI/SNRI and ozanimod, an additional analysis was performed to identify broad search events from >1 day to ≤ 6 weeks of the start date of concomitant use (narrow window), as steady-state plasma concentrations of commonly used SSRIs/SNRIs are achieved within that period.^{14,18}

Results

Study population

A total of 2257 participants from the phase 3 studies (SUNBEAM (1203/2257; 53.3%); RADIANCE (1054/2257; 46.7%)) entered DAYBREAK. Participants were a mean (standard deviation (SD)) age of 37.3 (9.1) years and most were women (66.5%), white (99.4%), and from Eastern Europe (90.9%) (Table 1). The mean (SD) age at MS symptom onset was 29.3 (8.8) years, age at MS diagnosis was 32.4 (9.0) years, and Expanded Disability Status Scale score was 2.6 (1.1). Mean (SD) exposure to ozanimod during DAYBREAK was 56.1 (15.3) months and total exposure was 10,540 person-years. Of the 2256 participants in DAYBREAK who received study drug, 274 (12.1%) used an SSRI/SNRI. Trazodone hydrochloride, escitalopram, sertraline hydrochloride, and escitalopram oxalate were among the most frequently ($\geq 10\%$) used SSRI/SNRIs (Table 1). The 274 participants were exposed to ≥ 1 SSRI/SNRI for a mean (SD) of 37.0 (24.6) months during DAYBREAK; the total concomitant SSRI/SNRI and ozanimod exposure was 845 person-years.

TEAEs included in the SA narrow MedDRA search

No participant had a TEAE matching the SA narrow search terms.

Table 1. Demographics and clinical characteristics of participants from the phase 3 SUNBEAM and RADIANCE studies who enrolled in the DAYBREAK open-label extension trial.

Characteristic	Ozanimod 0.92 mg (<i>N</i> = 2257 ^a)
Age, years	
Mean (SD)	37.3 (9.1)
Sex	
Men	755 (33.5)
Women	1502 (66.5)
Race	
White	2244 (99.4)
Black	9 (0.4)
Asian	1 (<0.1)
Other	3 (0.1)
BMI, ^b kg/m ²	
Mean (SD)	24.2 (4.7)
BMI category ^b	
<30 kg/m ²	2022 (89.6)
Time since MS symptom onset, years	
Mean (SD)	6.8 (6.2)
Concomitant SSRI/SNRI use	274 (12.1)
Trazodone hydrochloride	54 (19.7) ^c
Escitalopram	52 (19.0) ^c
Sertraline hydrochloride	49 (17.9) ^c
Escitalopram oxalate	30 (11.0) ^c
Venlafaxine hydrochloride	25 (9.1) ^c
Sertraline	24 (8.8) ^c
Fluoxetine hydrochloride	23 (8.4) ^c
Fluoxetine	22 (8.0) ^c
Paroxetine	22 (8.0) ^c
Venlafaxine	16 (5.8) ^c
Duloxetine	14 (5.1) ^c
Citalopram	13 (4.7) ^c
Paroxetine hydrochloride	12 (4.4) ^c
Citalopram hydrobromide	11 (4.0) ^c
Duloxetine hydrochloride	5 (1.8) ^c
Vortioxetine hydrobromide	4 (1.5) ^c
Desvenlafaxine	2 (0.7) ^c
Fluvoxamine maleate	2 (0.7) ^c
Trazodone	1 (0.4) ^c
Vortioxetine	1 (0.4) ^c

SD: standard deviation; BMI: body mass index; MS: multiple sclerosis; SSRI: selective serotonin reuptake inhibitor; SNRI: serotonin–norepinephrine reuptake inhibitor.

Data are presented as *n* (%) at DAYBREAK baseline, unless otherwise indicated.

^aOne participant did not receive study drug.

^bAt parent study baseline.

^cPercentage based on participants on an SSRI/SNRI medication.

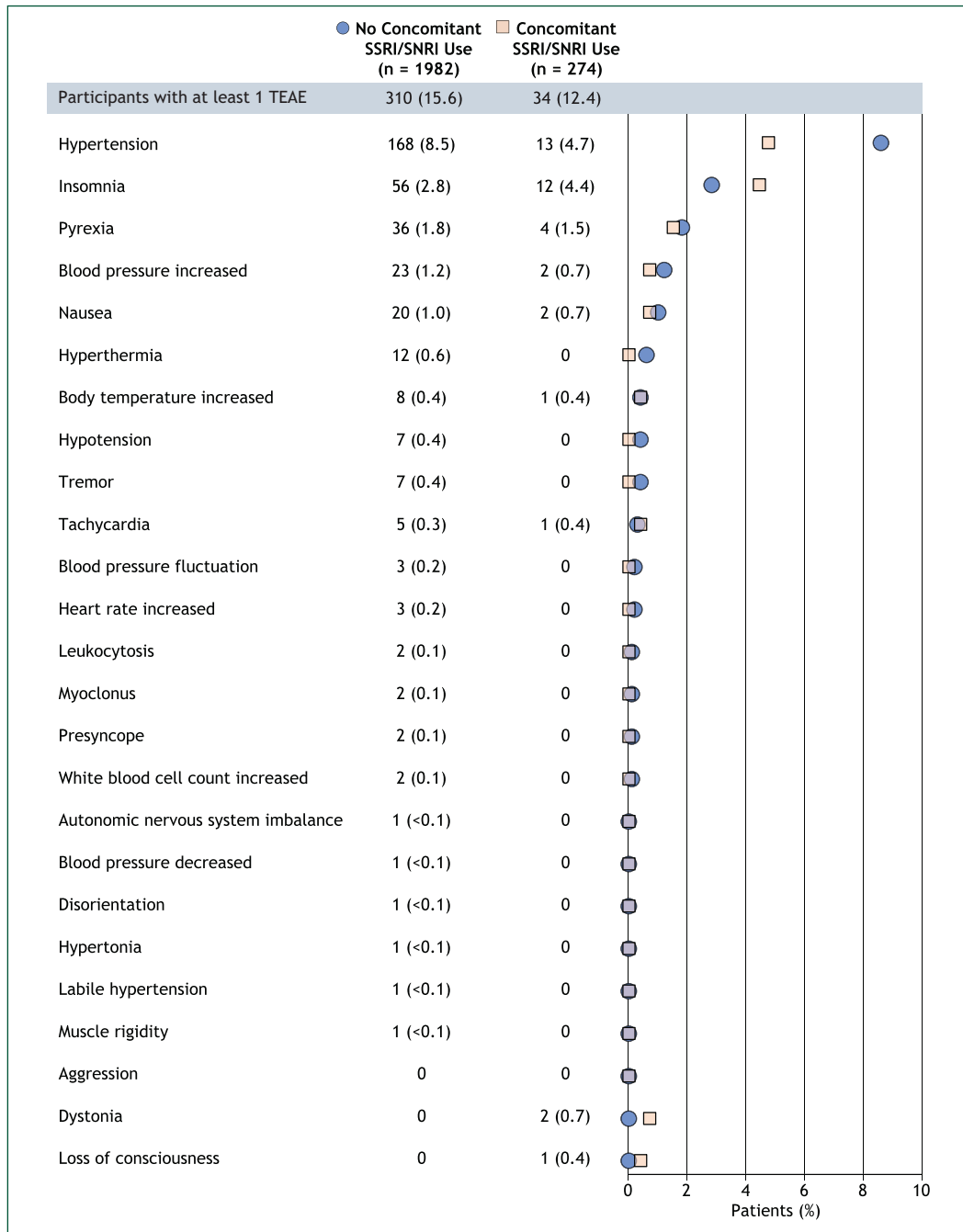


Figure 1. Overall incidence of TEAEs identified using the SA broad MedDRA search. Data are presented as *n* (%). MedDRA: Medical Dictionary for Regulatory Activities; SA: serotonin accumulation; SNRI: serotonin–norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor; TEAE: treatment-emergent adverse event.

TEAEs included in the SA broad MedDRA search

The proportion of DAYBREAK participants with ≥ 1 TEAE matching the SA broad search and broad timing window with terms potentially related to SA was 34/274 (12.4%) for those with concomitant SSRI/SNRI use and 310/1982 (15.6%) for those without concomitant SSRI/SNRI use (Figure 1); the difference (95% confidence interval) in the proportions of

participants with ≥ 1 TEAE (–3.2% (–7.5, 1.0)) was not nominally significant ($p=0.1630$). In the SA broad search, hypertension was the most common TEAE identified in participants with (4.7%) and without (8.5%) concomitant SSRI/SNRI use (Figure 1). Using the SA broad search criteria, the incidence of new TEAEs potentially related to SA remained relatively similar from >1 day to ≤ 6 weeks after the start date of

Table 2. Incidence of new TEAEs over time from >1 day after the start of concomitant SSRI/SNRI and ozanimod use per the SA broad MedDRA search.

TEAE preferred term	Concomitant SSRI/SNRI use (<i>n</i> =274)			
	>1 day to ≤2 weeks	>2 weeks to ≤4 weeks	>4 weeks to ≤6 weeks	>6 weeks
Number of participants with ≥1 TEAE	0	0	1 (0.4)	33 (12.0)
Hypertension	0	0	0	13 (4.7)
Insomnia	0	0	1 (0.4)	11 (4.0)
Pyrexia	0	0	0	4 (1.5)
Blood pressure increased	0	0	0	2 (0.7)
Dystonia	0	0	0	2 (0.7)
Nausea	0	0	0	2 (0.7)
Body temperature increased	0	0	0	1 (0.4)
Loss of consciousness	0	0	0	1 (0.4)
Tachycardia	0	0	0	1 (0.4)

TEAE, treatment-emergent adverse event; SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin–norepinephrine reuptake inhibitor; SA, serotonin accumulation; MedDRA, Medical Dictionary for Regulatory Activities.
Data are presented as *n* (%).

combination ozanimod and SSRI/SNRI treatment (0%–0.4% of participants had ≥1 TEAE, respectively) (Table 2). The incidence of most potentially SA-related TEAEs (12.0% of participants with concomitant SSRI/SNRI use) was >6 weeks after the start of concomitant use, the most common being hypertension (4.7%) followed by insomnia (4.0%) (Table 2). Two SA broad search TEAEs (hypertension, hypotension) led to or prolonged hospitalization in the group of participants who did not use an SSRI/SNRI concomitantly with ozanimod; no TEAEs required or prolonged hospitalization in the group of participants concomitantly using an SSRI/SNRI with ozanimod.

When considering the treatment of participants prior to DAYBREAK among the participants who did not use an SSRI/SNRI concomitantly with ozanimod in DAYBREAK, 103/638 (16.1%) who received interferon (IFN) β-1a and 207/1344 (15.4%) who received ozanimod in SUNBEAM or RADIANCE prior to entering the DAYBREAK OLE experienced a TEAE matching the SA broad search. Of the participants who used an SSRI/SNRI concomitantly with ozanimod in DAYBREAK, 15/98 (15.3%) who received IFN β-1a and 19/176 (10.8%) who received ozanimod in RADIANCE or SUNBEAM prior to entering the DAYBREAK OLE experienced a TEAE matching the SA broad search.

Discussion

In this analysis of ozanimod-treated participants in the DAYBREAK OLE study, SA narrow and broad

MedDRA searches did not identify any evidence of increased incidence of TEAEs potentially related to SA with concomitant SSRI/SNRIs use compared with those not using SSRI/SNRIs. TEAEs potentially related to SA were not clustered around the start of concomitant use.

Serotonin reuptake inhibitors and MAO inhibitors increase serotonin concentrations by preventing the transport of serotonin from the synapse back into the presynaptic terminal to be degraded or slowing the breakdown of serotonin, respectively.⁶ Although MAO-A inhibitors are more likely to cause serotonin toxicity,⁶ there is hypothetical concern of SA with use of SSRIs/SNRIs and MAO-B inhibitors. Clinical evidence of an interaction between serotonergic agents and MAO-B inhibitors is weak, and the incidences of toxic SA are exceedingly low, with concomitant use of these agents (rasagiline and selegiline) being generally well tolerated.^{19–23} Importantly, these agents were developed as MAO-B inhibitors as their primary mechanism of action.

The current analysis has limitations. First, a small subset of participants in DAYBREAK used an SSRI/SNRI and use was not systematic. The majority of the study population was white; therefore, these results may not be applicable to all patients, considering differences in the susceptibility of different racial groups to SA.²⁴ In addition, there is a potential for overestimation of risk based on the number of sensitive but nonspecific preferred terms in the SA broad MedDRA search. Ozanimod, along with the

other 5HT_{2A} receptor modulators, has a known risk of increasing blood pressure and is associated with hypertension in a subset of patients. Finally, DAYBREAK was not designed to specifically assess a potential interaction between ozanimod and SSRI/SNRI use; therefore, the current analysis should be interpreted as a descriptive observation of TEAEs that occurred without a prespecified study hypothesis regarding this topic.

In summary, symptoms related to SA were not associated with concomitant use of ozanimod and SSRI/SNRIs in the DAYBREAK participant cohort.

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Author Contributions

All authors contributed to and approved this manuscript.

Data Sharing

BMS policy on data sharing may be found at <https://www.bms.com/researchers-and-partners/independent-research/data-sharing-request-process.html>.

Declaration of Conflicting Interests

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Supplemental Material

Supplemental material for this article is available online.

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