Assessment of real-world adverse events associated with ozanimod in relapsing remitting multiple sclerosis

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Background

- Ozanimod is a disease-modifying therapy (DMT) approved by the US Food and Drug Administration (FDA) for the treatment of relapsing forms of multiple sclerosis
- Previous studies (eg, clinical trials, indirect treatment comparisons) have evaluated the comparative safety of ozanimod in relapsing remitting multiple sclerosis (RRMS) using clinical trial data
- However, only limited real-world evidence is available on the safety reporting of ozanimod
- To address this gap, the FDA Adverse Event Reporting System (FAERS) database was used to characterize ozanimod's real-world safety reporting relative to other RRMS therapies

The objectives of this study are:
- To describe ozanimod's spontaneous adverse event (AE) reporting as recorded in the FAERS database
- To compare ozanimod's spontaneous AE reporting with that of other DMTs used for RRMS

Methods

Data source

- The FAERS database is a spontaneous reporting database maintained by the FDA to support the organizations's postmarketing safety surveillance program for drug and therapeutic biologic products through data collection on adverse drug reactions[1]
- The data reported in the FAERS database include two principal sources:
  - Mandatory AE reports from pharmaceutical companies
  - Voluntary AE reports from healthcare professionals, patients, and manufacturers
- AEs reported from March 2020 were included, following ozanimod's approval. The dataset extends to September 2023, reflecting the most recent cutoff at the time of analysis. Reports without an AE date were excluded from the analysis
- For this analysis, we used data on patient demographics, administrative details, drug information, and outcomes associated with the reported AEs

Comparator drugs

- The comparator of interest was the group of all other DMTs approved for RRMS
- These other DMTs included dimethyl fumarate, monomethyl fumarate, diroximel fumarate, fingolimod, ponesimod, siponimod, teriflunomide cladribine, alemtuzumab, natalizumab, ocrelizumab, ublituximab, and ofatumumab

AEs of interest

- The analysis included comparisons based on ten individual AEs[a] selected from ozanimod's drug label, as well as two broader AE categories:
  - **Selected AEs:** The ten individual AEs treated as a single category
  - **AEs with serious outcomes:** All AE reports associated with serious outcomes[b]
- The specific AEs were captured in the FAERS data based on their corresponding "preferred terms" (PTs) or "high-level terms" (HLTs) fields
- The schematic here shows the relationship between "Selected AEs" and "AEs with serious outcomes" relative to all AE reports[c]

[a]The specific AEs considered included upper respiratory infection, hepatic transaminase elevation (elevated alanine and aspartate aminotransferase), orthostatic hypotension, urinary tract infection, back pain, hypertension, bradyarrhythmia and atrioventricular conduction delay, macular edema, herpes viral infection, and progressive multifocal leukoencephalopathy. [b]Serious outcomes defined as life-threatening AEs or those resulting in congenital anomaly, death, disability, hospitalization or required intervention to prevent permanent impairment/damage. [c]The figure is meant for illustrative purposes, and it is not drawn to scale.

Distribution of AEs

- To describe the distribution of different AEs reported for ozanimod, we calculated the percentage of reported AEs corresponding to each individual AE and each AE category (ie, selected AEs and AEs with serious outcomes)
- The percentages for ozanimod for each AE, **X**, and AE category, **Y**, were calculated as follows:

$$\%\ \text{of AE } \mathbf{X} \text{ for ozanimod} = \frac{\text{Number of AEs } \mathbf{X} \text{ reported for ozanimod}}{\text{Number of all AEs reported for ozanimod}}$$

$$\%\ \text{of AEs in category } \mathbf{Y} \text{ for ozanimod} = \frac{\text{Number of AEs reported for ozanimod in the Y category}}{\text{Number of all AEs reported for ozanimod}}$$

- A similar approach was used to describe the distribution of AEs for the comparator group (ie, all other DMTs)

Identification of signals of disproportionate reporting

- Reporting odds ratio (ROR)[2] was used to detect signals of disproportionate reporting for ozanimod vs all other DMTs, for each selected AE and AE category
- ROR is the ratio of a specific AE to all other AEs reported for the drug of interest (ozanimod) divided by the same ratio for all other DMTs in the comparator group:

	Ozanimod	All other DMTs
AE of interest	A	B
All other AEs	C	D

$$ROR = \frac{A/C}{B/D}$$

$$95\%CI = e^{\ln(ROR) \pm 1.96\sqrt{\left(\frac{1}{A}+\frac{1}{B}+\frac{1}{C}+\frac{1}{D}\right)}}$$

- A signal for significantly higher reporting for ozanimod is detected if the lower bound of the 95% CI > 1. A signal for significantly lower reporting is detected if the upper bound of the 95% CI < 1

Results

Summary of ozanimod reports

- Among 5665 reports (corresponding to 6576 AEs) listing ozanimod as the primary suspect drug, 73.3% involved multiple sclerosis (MS; excluding progressive forms). These MS-focused reports served as the basis for the current analysis
- In these reports, the mean patient age was 48.5 years, with 69% involving female patients and an average of 1.9 concomitant drugs used (**Table 1**)

Table 1. Summary of ozanimod reports

Data element	Statistic
Total number of reports	5665
Age, mean, years	48.5
Female, %	69
MS indication, %	73.3
Number of concomitant drugs, mean	1.9

Distribution of selected AEs for ozanimod and all other DMTs

- For ozanimod, upper respiratory tract infections, hypertension, and back pain had the highest reported percentage of the selected AEs with 26.5%, 26.7%, and 22.4%, respectively (**Figure 1**)
- For "all other DMTs," upper respiratory tract infections were the most frequently reported AE (40.5%), followed by urinary tract infections (20.3%) and herpes viral infections (11.8%) (**Figure 1**)

Distribution of AEs by serious vs nonserious outcomes for ozanimod vs all other DMTs

- The distribution of AEs by serious vs nonserious associated outcomes indicates that ozanimod had lower percentage of reported AEs associated with serious outcomes (14%) compared with "all other DMTs" used for RRMS (27%) (**Figure 2**)

Figure 1. Distribution of the selected AEs for ozanimod and all other DMTs used for RRMS

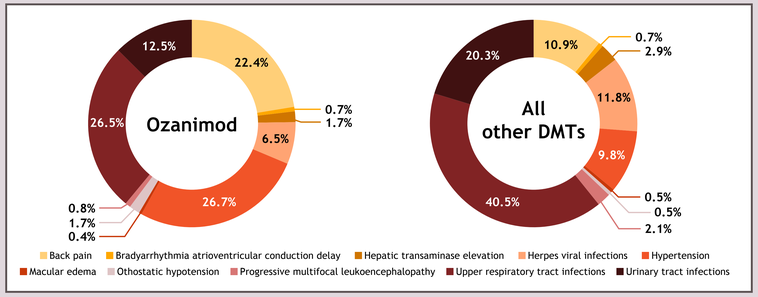
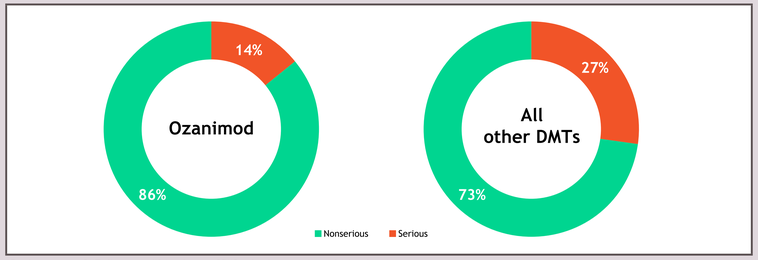


Figure 2. Distribution of AEs by serious vs nonserious outcomes for ozanimod vs all other DMTs



AE, adverse event; DMT, disease-modifying therapy; RRMS, relapsing remitting multiple sclerosis.

Signals of disproportionate reporting for ozanimod vs all other DMTs

- Analysis of the selected AEs suggests that ozanimod had a larger reporting rate of these AEs than all the other DMTs (ROR = 1.30), particularly for back pain, hypertension, and orthostatic hypotension, as to be expected given ozanimod's label (**Table 2**)
- However, ozanimod had a lower reporting rate (ROR < 1) relative to "all other DMTs" for certain AEs, such as for upper respiratory tract infections and urinary tract infections
- When considering AEs associated with serious outcomes, ozanimod had a significantly lower reporting rate compared with "all other DMTs" (ROR = 0.42)

ROR for ozanimod vs all other DMTs

Table 2. Signal scores for ozanimod vs all other DMTs

Data element	Number of AEs reported for ozanimod	ROR vs all other DMTs used for RRMS
Adverse events		
Back pain	106	2.68 (2.19-3.27)**
Bradyarrhythmia and atrioventricular conduction delay	3	1.03 (0.33-3.23)
Hepatic transaminase elevation	8	0.78 (0.38-1.56)
Herpes viral infections	31	0.71 (0.50-1.01)
Hypertension	126	3.53 (2.94-4.25)**
Macular edema	2	0.88 (0.22-3.56)
Orthostatic hypotension	8	3.55 (1.71-7.34)**
Progressive multifocal leukoencephalopathy	4	0.51 (0.19-1.38)
Upper respiratory tract infections	125	0.84 (0.70-1.00)*
Urinary tract infections	59	0.79 (0.61-1.02)
All selected AEs, grouped	472	1.30 (1.18-1.43)**
AEs associated with serious outcomes, grouped	902	0.42 (0.39-0.45)*

Each cell displays ROR (95% CI).
* Indicates that the percentage of reporting for the AE is disproportionately *lower* for ozanimod vs. the comparator (upper bound of 95% CI < 1).
** Indicates that the percentage of reporting for the AE is disproportionately *higher* for the ozanimod vs the comparator (lower bound of 95% CI > 1).
No asterisk indicates no signal was detected.
AE, adverse event; DMT, disease-modifying therapy; ROR, reporting odds ratio; RRMS, relapsing remitting multiple sclerosis.

Limitations

- As with any spontaneous reporting system, there may be underreporting, inconsistent reporting practices over time, limited patient details (including exposure duration), and uncertainty regarding the representativeness of reported events. These factors can bias results and limit generalizability
- Additionally, because ozanimod was approved in March 2020, the FAERS data were restricted to 2020–2023 to minimize bias from evolving reporting patterns; however, this approach also precludes older data for other DMTs
- Finally, the FAERS data lack information on the total number of people exposed to a drug, which is needed to calculate incidence rates of selected AEs. Hence, the results cannot be interpreted as comparisons of rates of AEs

Conclusions

- Based on this descriptive analysis of the FAERS data, ozanimod has a lower percentage of AEs linked to serious outcomes than the other DMTs
- In terms of signals of disproportionate reporting, ozanimod generally had a larger reporting proportion of the ten labeled AEs compared with the other DMTs; however, when considering AEs associated with serious outcomes, ozanimod had a significantly lower reporting rate compared with all other DMTs used for RRMS

References

1. Center for Drug Evaluation and Research. FDA's Adverse Event Reporting System (FAERS). https://www.fda.gov/drugs/surveillance/questions-and-answers-fdas-adverse-event-reporting-system-faers. Accessed October 31, 2023.
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Disclosures

DP: Employee and/or shareholder of Bristol Myers Squibb at the time of this analysis
LN'D: Employee and/or shareholder of Bristol Myers Squibb
ES, OPL, AF, and **HA:** Employees of Analysis Group, a company that received fees from Bristol Myers Squibb for the conduct of this research

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