Brain Volume Changes During 3 to 5 Years of Ozanimod in Relapsing MS

ID56

Douglas L. Arnold,[1] James K. Sheffield,[2] Xavier Montalban,[3] Bruce A. C. Cree,[4] Ludwig Kappos,[5] Giancarlo Comi,[6] Hans-Peter Hartung,[7] Hongjuan Liu,[2] Chahin Pachai,[2] Diego Silva,[2] Jeffrey A. Cohen[8]

[1]NeuroRx Research and Montréal Neurological Institute, McGill University, Montréal, Quebec, Canada; [2]Bristol Myers Squibb, Princeton, New Jersey; [3]Department of Neurology-Neuroimmunology, Centre d'Esclerosi Múltiple de Catalunya (Cemcat), Hospital Universitario Vall d'Hebron, Barcelona, Spain; [4]Weill Institute for Neurosciences, Department of Neurology, University of California San Francisco, San Francisco, California; [5]Research Center for Clinical Neuroimmunology and Neuroscience Basel (RC2NB), Departments of Head, Spine and Neuromedicine, Clinical Research, Biomedicine, and Biomedical Engineering, University Hospital and University of Basel, Basel, Switzerland; [6]Vita-Salute San Raffaele University and Casa di Cura del Policlinico, Milan, Italy; [7]Department of Neurology, Medical Faculty, Heinrich-Heine University, Düsseldorf, Germany; Brain and Mind Centre, University of Sydney, Sydney, Australia; Department of Neurology, Medical University of Vienna, Vienna, Austria; Palacky University Olomouc, Olomouc, Czech Republic; [8]Mellen Center for MS Treatment and Research, Cleveland Clinic, Cleveland, Ohio

Background

- Compared with healthy persons, patients with relapsing multiple sclerosis (RMS) experience an accelerated rate of brain volume loss, particularly in the presence of disease activity[1]
- Brain volume loss correlates with long-term disability progression and cognitive impairment in RMS[2,3]
- Ozanimod, a sphingosine 1-phosphate (S1P) receptor modulator that binds with high affinity selectively to S1P receptor subtypes 1 and 5, is approved in multiple countries for the treatment of adults with RMS and is approved for the treatment of moderately to severely active ulcerative colitis in the United States[4-6]
- In the randomized, double-blind, phase 3 SUNBEAM (NCT02294058) and RADIANCE (NCT02047734) trials, ozanimod reduced whole brain volume (WBV), thalamic volume (TV), and cortical grey matter volume (CGMV) loss in participants with RMS compared with intramuscular interferon (IFN) ß-1a[7,8]

Objective

- To evaluate WBV, TV, and CGMV loss among SUNBEAM and RADIANCE participants who entered an ongoing open-label extension (OLE) study (DAYBREAK; NCT02576717)

Methods

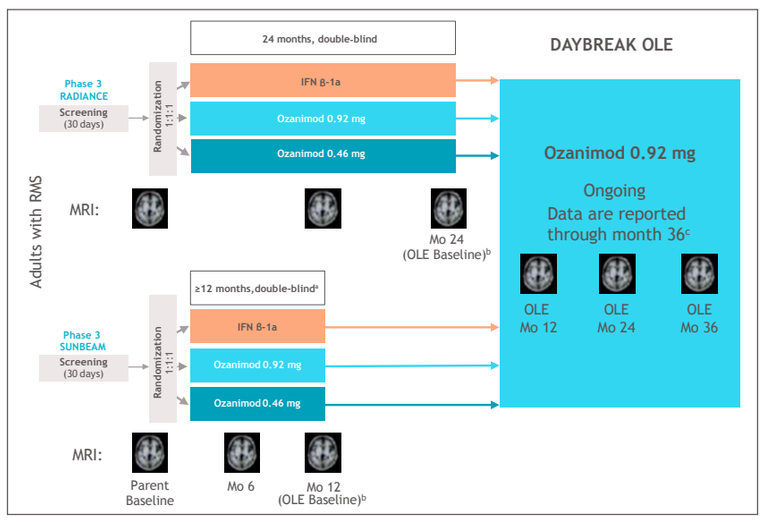
Study design and participants

- Adults with RMS who completed one of the phase 3 ozanimod trials (SUNBEAM [≥ 12 months] and RADIANCE [24 months]) were eligible to enroll in DAYBREAK (**Figure 1**)
  - Participants with RMS who completed phase 1 or 2 trials of ozanimod were also eligible for DAYBREAK, but are not included in this analysis of brain volume
- In the parent trials, oral ozanimod was up-titrated to a dose of 0.46 or 0.92 mg/d and IFN ß-1a was administered at a dosage of 30 µg intramuscular weekly
  - Ozanimod was initiated at a dose of 0.23 mg/d (equivalent to ozanimod HCl 0.25 mg) on days 1–4, ozanimod 0.46 mg/d (equivalent to ozanimod HCl 0.5 mg) on days 5–7, and the assigned dose of ozanimod 0.46 or 0.92 mg/d (equivalent to ozanimod HCl 1 mg) starting on day 8 of ozanimod treatment
- In DAYBREAK, all participants received ozanimod 0.92 mg/d
- Baseline WBV and CGMV were quantified via SienaX and TV was quantified using locally developed software based on automatic nonlinear image matching and anatomical labeling (ANIMAL) and intensity normalized stereotaxic environment for the classification of tissue (INSECT)[9]; percentage change from baseline was quantified via JacobianAtrophy software using Jacobian integration[10]

Statistics

- Least squares (LS) mean percentage changes in WBV, TV, and CGMV from parent trial baseline were estimated using mixed model for repeated measures (MMRM)
  - Model included percentage change from parent trial baseline in brain volume as the dependent variable, and stratification factors (region [Eastern Europe vs rest of world], baseline Expanded Disability Status Scale category [≤ 3.5 vs > 3.5]), treatment, time point, and the interaction between treatment and time point as fixed effects, parent trial baseline brain volume as a continuous covariate, and subject as a random effect
- For analyses of annualized rates of WBV, TV, and CGMV loss, LS means and between-treatment differences were estimated using MMRM
  - Model included annualized atrophy rate from parent or OLE baseline (as appropriate) as the dependent variable, and the stratification factors and the interaction between treatment and time point as fixed effects, parent or OLE baseline (as appropriate) as a continuous covariate, and subject as a random effect
- An unstructured covariance was used to model within-subject errors for both analyses
- *P* values presented herein are nominal, as treatment comparisons in this post hoc, exploratory analysis were not subject to multiplicity adjustment

Figure 1. Study design



[a]All SUNBEAM participants remained on treatment until the last participant completed 12 months. [b]The final MRI from the parent trial was used as the "OLE baseline" scan unless it was performed ≥ 6 months prior to entry into DAYBREAK, in which case a new baseline scan was obtained. [c]December 2020 data cutoff. IFN, interferon; MRI, magnetic resonance imaging; OLE, open-label extension; RMS, relapsing multiple sclerosis.

Results

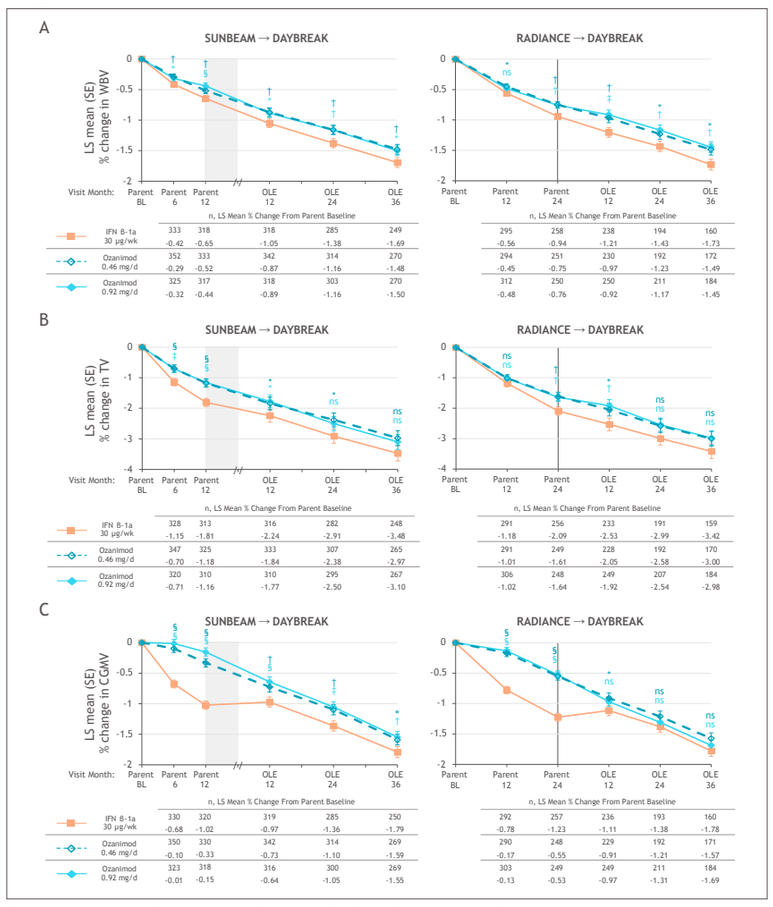
Participants

- Of 2666 participants enrolled in SUNBEAM or RADIANCE, 2394 completed a phase 3 parent trial and 2257 entered DAYBREAK (IFN ß-1a: n = 741; ozanimod 0.46 mg: n = 756; ozanimod 0.92 mg: n = 760)

Mean change from baseline in brain volume

- In both parent trials, WBV loss from baseline was less in participants who received ozanimod than in participants who received IFN ß-1a (**Figure 2A**)
  - These beneficial effects were maintained in DAYBREAK in participants continuously treated with ozanimod
  - WBV loss slowed after switching from IFN ß-1a to ozanimod in DAYBREAK, but remained greater in participants who started treatment with IFN ß-1a
- Results were similar for WBV and TV loss; however, the volume loss was nearly twice as great for TV than for WBV (**Figure 2B**)
  - Differences between treatment groups during the parent trials appear larger for TV loss versus WBV loss
- The difference between treatment groups was much greater for CGMV loss (**Figure 2C**) than for WBV or TV loss

Figure 2. Whole brain volume loss (A), thalamic volume loss (B), and cortical grey matter volume loss (C) relative to *parent trial* baseline

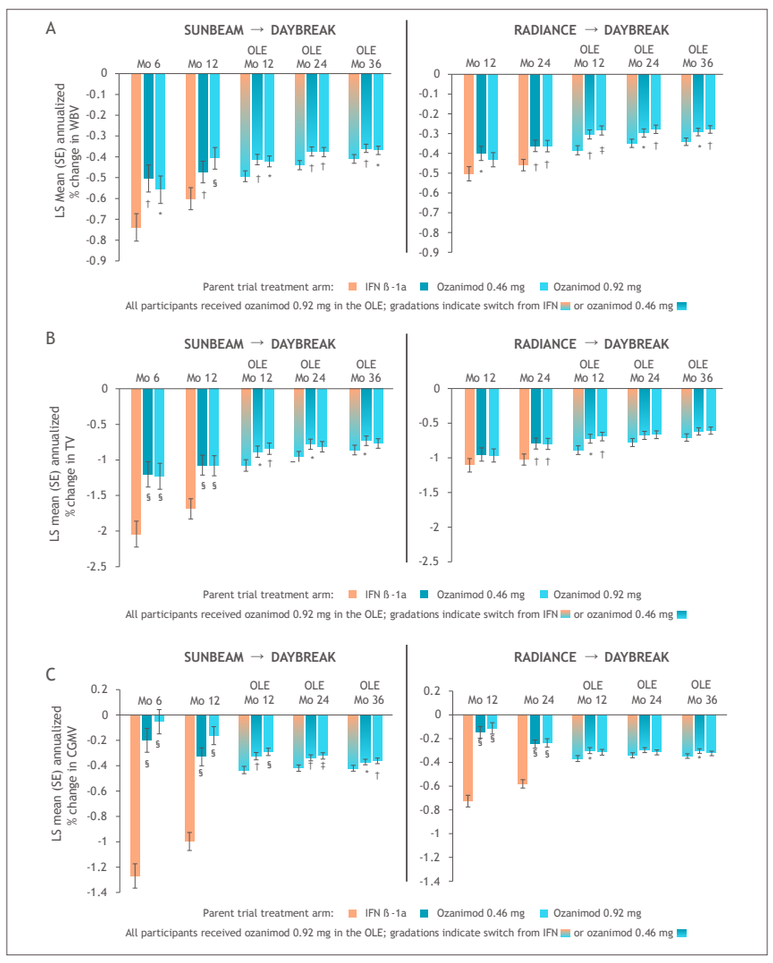


*P < 0.05; †P < 0.01; ‡P < 0.001; §P < 0.0001 vs IFN ß-1a. BL, baseline; CGMV, cortical grey matter volume; IFN, interferon; LS, least squares; ns, not statistically significant (P ≥ 0.05); OLE, open-label extension (DAYBREAK); SE, standard error; TV, thalamic volume; WBV, whole brain volume.

Mean annualized change from baseline in brain volume

- Relative to parent trial baseline
  - Annualized percentage change in WBV slowed over 2-3 years in the OLE, when all participants received ozanimod 0.92 mg/d (**Figure 3A**)
    - LS mean annualized percentage change decreased from approximately 0.4%-0.5% at the beginning of the parent trials to approximately 0.3%-0.4% by OLE month 36
  - Rates for TV loss were approximately twice as great as WBV loss and showed a similar proportional decrease over time (**Figure 3B**)
    - The accelerated atrophy among participants who initially received IFN ß-1a was greater for TV than for WBV
  - Compared with participants who initially received IFN ß-1a, the difference in the rate of loss among participants who received ozanimod was even more marked for CGMV (**Figure 3C**)
    - Early changes with ozanimod appear to be less than the subsequent average of 0.3%-0.4% per year
    - Early changes with IFN ß-1a in the parent trials are much greater than the subsequent average when all participants were receiving ozanimod 0.92 mg/d in the OLE

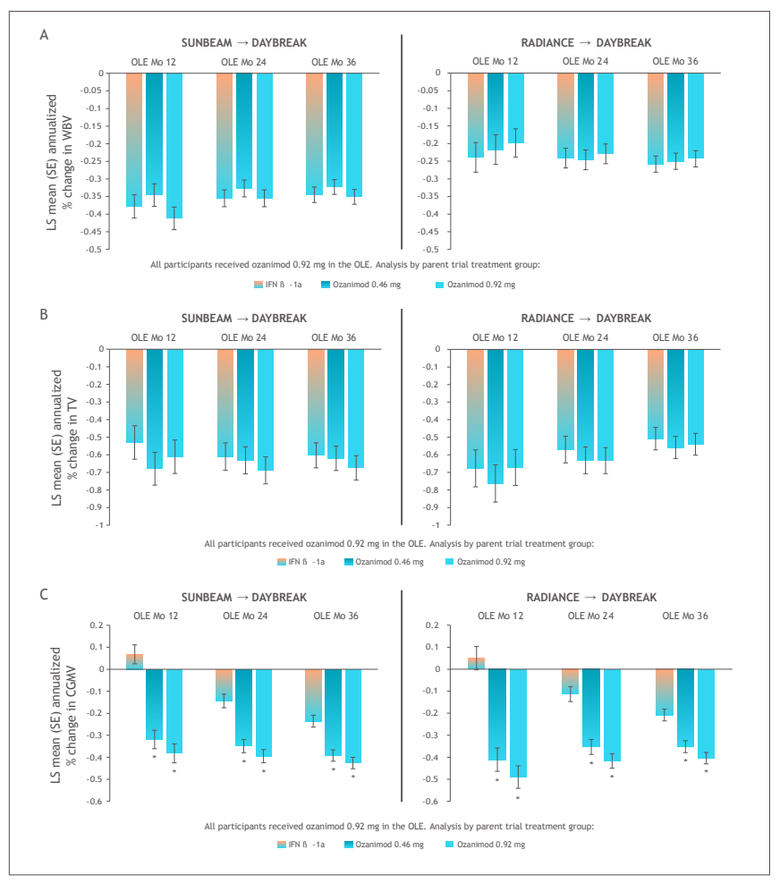
Figure 3. Annualized whole brain volume loss (A), thalamic volume loss (B), and cortical grey matter loss (C) relative to *parent trial* baseline



*P < 0.05; †P < 0.01; ‡P < 0.001; §P < 0.0001 vs IFN ß-1a. CGMV, cortical grey matter volume; IFN, interferon; LS, least squares; OLE, open-label extension (DAYBREAK); SE, standard error; TV, thalamic volume; WBV, whole brain volume.

- Relative to OLE baseline
  - Annualized percentage changes in WBV and TV loss were similar among participants who received continuous ozanimod and for those who switched from IFN ß-1a to ozanimod in DAYBREAK (**Figure 4A** and **4B**)
  - There was an initial increase followed by a slight decline in CGMV relative to OLE baseline among participants who switched from IFN ß-1a to ozanimod in DAYBREAK (**Figure 4C**), which may be reflective of direct CNS effects of ozanimod

Figure 4. Annualized whole brain volume loss (A), thalamic volume loss (B), and cortical grey matter loss (C) in the OLE relative to *OLE* baseline[a]



*P < 0.0001 vs IFN ß-1a.
[a]OLE baseline was the last available MRI scan during the parent trial; a separate baseline MRI was obtained only if the last available scan was ≥ 6 months prior to OLE enrollment. CGMV, cortical grey matter volume; IFN, interferon; LS, least squares; MRI, magnetic resonance imaging; OLE, open-label extension (DAYBREAK); SE, standard error; TV, thalamic volume; WBV, whole brain volume.

Discussion

- The greater between-treatment differences for CGMV (**Figure 2C**) compared with WBV or TV is likely a result of 2 opposing phenomena; in the parent trials:
  - Participants who received ozanimod experienced an early preservation of CGMV (indicated by the minimal decline or slight increase of the blue curves in **Figure 2C**)
  - Participants who received IFN ß-1a experienced a reversible, accelerated loss of CGMV (indicated by the initial steep decline of the orange curve in **Figure 2C**)
  - The positive slope of the orange curve from the end of the parent trials to month 12 of the OLE indicates an increase in CGMV after switching from IFN ß-1a to ozanimod, and an early effect of ozanimod on preserving CGMV

Conclusions

- In the parent trials, the rates of brain volume loss were less in ozanimod-treated participants than IFN ß-1a–treated participants, and the beneficial effects were maintained in the OLE in participants continuously treated with ozanimod
- Switching from IFN ß-1a to ozanimod in the OLE reduced the annualized rates of WBV, TV, and CGMV loss
  - CGMV was particularly preserved, possibly reflecting direct CNS effects of ozanimod
- Global and regional brain volume loss after 4-5 years of follow-up remained less in participants continuously treated with ozanimod compared with participants who started on IFN ß-1a

References

1. Giovanni G, et al. *Mult Scler Relat Disord* 2016;9:S5-S48. **2.** Sormani MP, et al. *Ann Neurol* 2014;75:43-49. **3.** Batista S, et al. *J Neurol* 2012;259:139-146. **4.** ZEPOSIA® (ozanimod) [package insert]. Princeton, NJ: Bristol Myers Squibb; May 2021. **5.** ZEPOSIA® (ozanimod) [product monograph]. Mississauga, ON: Celgene Inc; October 2020. **6.** ZEPOSIA® (ozanimod) [summary of product characteristics]. Utrecht, Netherlands: Celgene Distribution BV; 2020. **7.** Comi G, et al. *Lancet Neurol* 2019;18:1009-1020. **8.** Cohen JA, et al. *Lancet Neurol* 2019;18:1021-1033. **9.** Collins DL, et al. *Hum Brain Mapp* 1995;3:190-208. **10.** Nakamura K, et al. *Neuroimage Clin* 2014;4:10-17.

Acknowledgments

- We thank the patients and families who made these studies possible, the clinical study teams who participated, and NeuroRx for analyzing the MRIs and performing the analysis of brain volume
- The SUNBEAM, RADIANCE, and DAYBREAK studies were supported by Celgene International II
- All authors contributed to and approved the poster. Writing and editorial assistance was provided by Jessica D. Herr, PharmD of Peloton Advantage, LLC, an OPEN Health company, and was funded by Bristol Myers Squibb

Disclosures

DLA: personal fees for consulting and/or grants from Albert Charitable Trust, Alexion Pharma, Biogen, Celgene, Frequency Therapeutics, Genentech, Med-Ex Learning, Merck Serono, Novartis, Population Council, Roche, and Sanofi-Aventis; grants from Biogen, Immunotec, and Novartis; and an equity interest in NeuroRx. **JKS:** employee and shareholder of Bristol Myers Squibb **XM:** speaking honoraria and travel expenses for participation in scientific meetings, has been a steering committee member of clinical trials, or participated in advisory boards of clinical trials in the past 3 years with Actelion, Alexion, Bayer, Biogen, Bristol Myers Squibb/Celgene, EMD Serono, EXCEMED, Genzyme, Hoffmann-La Roche, Immunic, Janssen Pharmaceuticals, MedDay, Merck, MSIF, Mylan, Nervgen, NMSS, Novartis, Roche, Sanofi-Genzyme, Teva Pharmaceuticals, and TG Therapeutics **BACC:** personal compensation for consulting for Alexion, Atara, Autobahn, Avotres, EMD Serono, Novartis, Sanofi, TG Therapeutics, and Therini, and received grant support from Genentech **LK:** institutional research support: steering committee, advisory board, and consultancy fees: Actelion, Bayer HealthCare, Biogen, Bristol Myers Squibb, Genzyme, Janssen, Japan Tobacco, Merck, Novartis, Roche, Sanofi, Santhera, Shionogi, and TG Therapeutics; speaker fees: Bayer HealthCare, Biogen, Merck, Novartis, Roche, and Sanofi; support of educational activities: Allergan, Bayer HealthCare, Biogen, CSL Behring, Desitin, Genzyme, Merck, Novartis, Roche, Pfizer, Sanofi, Shire, and Teva; license fees for Neurostatus products; and grants: Bayer HealthCare, Biogen, European Union, Innosuisse, Merck, Novartis, Roche, Swiss MS Society, and Swiss National Research Foundation **GC:** compensation for consulting and/or speaking activities from Almirall, Biogen, Celgene, EXCEMED, Forward Pharma, Genzyme, Merck, Novartis, Roche, Sanofi, and Teva **HPH:** personal fees for consulting, serving on steering committees, and speaking from Bayer Healthcare, Biogen, Celgene, GeNeuro, Genzyme, Merck, MedImmune, Novartis, Octapharma, Roche, Sanofi, and Teva **HL, CP, DS:** employees and shareholders of Bristol Myers Squibb **JAC:** personal compensation for consulting for Adamas, Atara, Bristol Myers Squibb, Convelo, MedDay, and Mylan; and serving as an Editor of *Multiple Sclerosis Journal*

Presented at the 29th Annual Meeting of the European Charcot Foundation; 14-18 November 2021; Baveno, Italy
Previously presented at the Consortium of Multiple Sclerosis Centers; October 25–28, 2021; Orlando, Florida and the European Academy of Neurology; June 10-22, 2021, Virtual Meeting

Email: douglas.arnold@mcgill.ca