Full Title: Ozanimod demonstrates preservation of brain volume at 1 and 2 years in two phase 3 trials of relapsing multiple sclerosis (SUNBEAM and RADIANCE)

Short Title (39 characters; limit of 45 characters): Brain volume preservation with ozanimod

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Background: Ozanimod (RPC1063) is an oral once-daily immunomodulator that selectively targets sphingosine 1-phosphate 1 and 5 receptors. Brain volume loss (BVL) is thought to correlate with and predict disability and be a marker of long-term disease progression and cognitive impairment; reducing BVL is an important treatment goal.

Methods: SUNBEAM (NCT02294058) and RADIANCE Part B (NCT02047734) were two similarly-designed phase 3, randomised, double-blind, double-dummy, active-controlled, parallel-group studies of the efficacy (primary outcome annualised relapse rate) and safety of once-daily ozanimod HCl 1 mg or 0.5 mg vs intramuscular interferon beta-1a (IFN) 30 µg for ≥12 months (m) (SUNBEAM, n=1346) or 24 m (RADIANCE, n=1313) in relapsing multiple sclerosis (RMS). BVL was evaluated using the Jacobian integration method to assess changes in normalised whole brain, cortical grey matter, and thalamic volumes (rank analysis of covariance, percent reductions in median percent BVL from baseline).

Results: Baseline brain volumes were similar across treatment groups. Ozanimod 1 mg and 0.5 mg demonstrated slowing of whole BVL vs IFN: 32.5% ($p<0.0001$) and 12.3% ($p=0.0615$), respectively in SUNBEAM (12 m); 26.6% ($p<0.0001$) and 24.5% ($p=0.0001$) in RADIANCE (24 m). Ozanimod 1 mg and 0.5 mg slowed cortical grey matter loss vs IFN: 83.8% ($p<0.0001$) and 61.4% ($p<0.0001$) in SUNBEAM; 58.3%

(p<0.0001) and 55.1% (p<0.0001) in RADIANCE. Ozanimod 1 mg and 0.5 mg demonstrated slowing of thalamic BVL vs IFN: 38.5% (p<0.0001) and 34.3% (p=0.0001) in SUNBEAM; 31.9% (p<0.0001) and 30.1% (p=0.0008) in RADIANCE.

Conclusion: Ozanimod resulted in significant reductions of normalised whole, cortical grey, and thalamic BVL in both studies at 12 and 24 m. This effect, combined with significant outcomes on other radiographic measures of disease activity and the known correlations between BVL and disability/cognitive impairment, suggest ozanimod may be beneficial in reducing tissue damage and longer-term disease worsening in RMS patients.