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Consistent reduction in the annualized rate of brain volume loss across phase 3 core and extension trials of fingolimod in relapsing multiple sclerosis

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Background/objective: In phase 3 trials, fingolimod 0.5 mg or 1.25 mg daily reduced brain atrophy versus placebo over 2 years (FREEDOMS and FREEDOMS II), and versus interferon beta-1a IM (IFNβ-1a) over 1 year (TRANSFORMS). Rates of brain atrophy on continuous fingolimod treatment were sustained in extension studies, but diminished number of completers might limit interpretability. We estimated the continuous effect of fingolimod treatment on brain volume (BV) loss, using all data from phase 3 and extension trials. Design/methods: We determined annualized percentage BV change (PBVC) for all patients individually, to account for variable treatment-time exposures. During phase 3 studies and extensions, annualized PBVC was calculated for each patient from fingolimod treatment initiation until last available scan. Descriptive analyses included cohorts of patients receiving fingolimod 0.5 mg continuously, and all patients receiving fingolimod (combined-dose group) continuously, for up to 60 months from phase 3 baseline. Further analyses, using these dose-group definitions, were also conducted for up to 24 months from extension baseline to compare annualized PBVC among patients after switching to fingolimod from placebo or IFNβ-1a, with that deter- mined on long-term fingolimod treatment.

Results: Respectively, mean annualized PBVC in the long-term continuous fingolimod 0.5 mg and combined- dose groups was FREEDOMS, ?0.45% (n=372), ?0.42% (n=718); FREEDOMS II, ?0.41% (n =279), ?0.38% (n=553); TRANSFORMS, ?0.31% (n=379), ?0.31% (n=728); and after switching was FREEDOMS, ?0.49% (n = 135), ?0.44% (n = 259); FREEDOMS II, ?0.47% (n = 47), ?0.43% (n = 103); TRANSFORMS, ?0.25% (n=130), ?0.19% (n=267).

Conclusion: Annualized PBVC during fingolimod phase 3 and extension studies demonstrate a consistent low rate of brain atrophy, supporting previous observations from individual studies. After switching to fingolimod from the comparator, patients exhibited similar atrophy rates to those initially randomized to fingolimod. Annualized PBVC calculation incorporates all available PBVC data, despite varying treatment-time exposures, and partly addresses discontinuation bias that may occur in long-term analyses.