Appendix e-1: Exposure-efficacy relationship analysis

The relationship between efficacy parameters and exposure to everolimus was assessed using linear mixed model with repeated measures to link the postbaseline average weekly seizure frequency to the time-normalized C_{min} (TN C_{min}) considering 12-week time intervals.

With respect to plasma exposure of everolimus, patients initially randomized to the everolimus high-exposure (HE) group continued to achieve a higher C_{min} in the extension phase compared with patients in the other randomization groups (placebo and everolimus low exposure [LE]). The median C_{min} (with n>1) ranged from 4.87 to 6.88 ng/mL among placebo-randomized patients initiating everolimus in the extension phase, 4.44 to 6.13 ng/mL for everolimus LE, and 5.30 to 9.22 ng/mL for everolimus HE groups. A linear-mixed model demonstrated that doubling of TN C_{min} was associated with a significant average reduction of 21.39% (95% CI, 13.3-28.74) over a 12-week interval period in postbaseline absolute seizure frequency. A 0.5-fold lower baseline seizure frequency was associated with 49.41% (95% CI, 45.68-52.89%) reduction in post-baseline absolute seizure frequency. Twelve additional weeks on treatment resulted in an additional 5.64% (95% CI, 3.54-7.7) reduction in postbaseline seizure frequency.

Exposure-efficacy analysis suggest that reductions in seizure frequency were both time and exposure dependent. Higher everolimus exposure, lower baseline seizure frequency, and longer treatment duration were associated with a lower postbaseline seizure frequency. The effect of longer treatment duration on further increases in efficacy appears to be modest.

Appendix e-2: Exposure-safety relationship analysis

The time to the first occurrence of selected AEs (stomatitis and infections) was fitted using an extended Cox model with interval time-normalized C_{min} (TN C_{min}) as a time varying covariate, stratified by age subgroup. Four time intervals were considered to adjust relative risks by the impact of exposure on safety: during the 6-week titration period, the 12 weeks of the maintenance period of the core phase, the first 8 weeks of the extension phase, and the extension phase (after week 26). TN C_{min} was presented for patients who reported at least 1 grade 3/4 AE and for those who had not reported any grade 3/4 AEs.

      Extended Cox regression analysis showed that a higher trough exposure (C_{min}) was not associated with a higher risk of the most common AEs including stomatitis (hazard ratio [HR], 1.00; 95% confidence interval [CI], 0.80-1.26), pyrexia (HR, 0.89; 95% CI, 0.65-1.23), diarrhea (HR, 1.26; 95% CI, 0.88-1.80), nasopharyngitis (HR, 0.98; 95% CI, 0.67-1.43), and upper respiratory tract infections (HR, 1.20; 95% CI, 0.81-1.79).