RESULTS

No systemic toxicity was associated with treatment during the 20 week study. No significant test article-related effects were observed on body weight, intraperitoneal pressure (CIP), clinical pathology parameters, organ weights, or macroscopic findings. Mild to moderate conjunctival hyperemia and chemosis were found in animals across all groups including the vehicle control group. Ocular histopathology showed no significant histological lesions in any eyes of the mid- and low-dose groups, except for a few test article-related perivascular episcleral infiltration and/or conjunctival aggregates of lymphocytes and plasma cells noted in 3 eyes (1 untreated, 1 vehicle treated and 1 mid-dose group). In the eyes treated with the high-dose test article, mild to moderate perivascular infiltrates within the retinal ganglion cell (RGC) layer and optic nerve head were noted in 5 of 5 eyes (Figure 2, panels A, B, C and D). Minimum to mild perivascular infiltrates in inner nuclear layer (INL) were also noted in 2 of these 5 eyes (animal ID Z592 OD and 2004 OD), and of these 2 eyes (2002 OD) clinical ocular signs of toxicity including choroidal neovascularization and near to complete loss of photoreceptors in the treated area (Figure 1, panels E & F). It was noted that minimal perivascular lymphocytic infiltrates were also observed within the RGC layer of the untreated contralateral eye of this animal (2012 OD).

RESULTS (CONTINUED)

Figure 5: Assessment of ONL integrity across treatment groups measured by histology and OCT. (A) Representative photomicrographs of the retinal morphology to compare the ONL thickness of treated (OD) and untreated (OS) eyes. (B) Scanning laser ophthalmoscopy with superimposed retinal blood vessels and optic nerve. (C) Reference (vehicle treated) OD and untreated contralateral eye OD with Z592 treatment. (D) Treated OD with high-dose treatment and (E) untreated contralateral OD (OS) across vehicle, low-, mid-, and high-dose group. Significance is based on comparison of treatment to vehicle control with *p < 0.05, **p < 0.01, ***p < 0.001, and ****p < 0.0001.

Figure 6: Representative photomicrographs of the retinal morphology to compare the ONL thickness of treated (OD) and untreated (OS) eyes. (A) Treated OD with high-dose treatment and (B) untreated contralateral OD (OS) across vehicle, low-, mid-, and high-dose group. Significance is based on comparison of treatment to vehicle control with *p < 0.05, **p < 0.01, ***p < 0.001, and ****p < 0.0001.

REFERENCES