Purpose: To evaluate the efficacy and safety of intravitreal aflibercept (IVT-AFL) compared with macular laser photocoagulation in patients with clinically significant diabetic macular edema (DME) enrolled in the VIVID-DME (Europe, Australia, and Japan) and VISTA-DME trials (US). Methods: Two randomised, multicentre, double-masked trials. Patients were randomised 1:1:1 to IVT-AFL 2 mg every 4 weeks (2q4) plus sham laser; IVT-AFL 2 mg every 8 weeks (2q8) (after 5 initial monthly doses) plus sham laser; or laser photocoagulation plus sham IVT treatment. From Week 24 additional active treatment was allowed (laser in the IVT-AFL arms/IVT-AFL in the laser arm) in the case of disease reoccurrence/persistence. The primary endpoint was the change from baseline in best-corrected visual acuity (BCVA) at Week 52. Results: 865 patients (VIVID-DME [n=404]; VISTA-DME [n=461]) were randomised and received study medication. Baseline demographics were similar. Both dosing regimens of IVT-AFL were statistically superior to laser treatment for the mean change in BCVA at Week 52 with improvements ranging between 10.5–12.5 letters (vs 0.2–1.2 letters for laser; \(P<0.0001\)). The 2q8 regimen demonstrated similar efficacy to 2q4 with fewer injections required. Overall, IVT-AFL was generally well tolerated with a similar incidence of adverse events (AEs) and serious AEs across all groups and no significant differences in the incidence of Antiplatelet Trialists’ Collaboration ATE events. Conclusions: IVT-AFL is an effective and well-tolerated treatment for DME, with significant effects on visual and anatomic outcomes. A 2q8 regimen appears to result in similar efficacy with decreased injection-related burden on patients, caregivers, physicians, and overall healthcare systems.