VEGF and CETP; VEGF and LIPC; VEGF and COL10A1; or VEGF and TNFRSF10A. In certain embodiments, bispecific antibodies may bind to two different epitopes of VEGF. Bispecific antibodies may also be used to localize cytotoxic agents to cells which express VEGF. Bispecific antibodies can be prepared as full length antibodies or antibody fragments (e.g., Fab, Fab', or Fab-C fragments).

[441] In some instances, the bispecific antibody is a bispecific anti-VEGF/anti-angiopoeitin 2 (Ang2) antibody disclosed in U.S. Patent Application No. US 2014/0017244, which is incorporated herein by reference in its entirety. For example, the anti-VEGF/anti-Ang2 bispecific antibody may include a first binding domain that binds VEGF (such as any of the anti-VEGF antibodies described herein) and a second binding domain that binds Ang2 that includes (a) an HVR-H1 comprising the amino acid sequence of GYYMH (SEQ ID NO: 61); (b) an HVR-H2 comprising the amino acid sequence of WINPNSGGTNYAQKFQG (SEQ ID NO: 62); (c) an HVR-H3 comprising the amino acid sequence of SPNPYYYDSSGYYYPGAFDI (SEQ ID NO: 63); (d) an HVR-L1 comprising the amino acid sequence of GGNNIGSKSVH (SEQ ID NO: 64); (e) an HVR-L2 comprising the amino acid sequence of DDSDRPS (SEQ ID NO: 65); and (f) an HVR-L3 comprising the amino acid sequence of QVWDSSSDHWV (SEQ ID NO: 66), or a combination of one or more of the above HVRs and one or more variants thereof having at least about 80% sequence identity (e.g., 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity) to any one of SEQ ID NOs: 61-66.

[442] In some instances, the anti-VEGF/anti-Ang2 bispecific antibody may include a first binding domain that binds VEGF (such as any of the anti-VEGF antibodies described herein) and a second binding domain that binds to Ang2. In some instances, the anti-VEGF/anti-Ang2 bispecific antibody may include a first binding domain that binds VEGF (such as any of the anti-VEGF antibodies described herein) and a second binding domain that specifically bind to Ang2, wherein the second binding domain is any antibody binding domain described in International Patent Application Publication No. WO 2010/069532, which is incorporated herein by reference in its entirety, or a variant thereof.

temperature of the rabbit vitreous. These data were subjected to a non-compartmental analysis to obtain pharmacokinetic (PK) parameters.

[583] The pharmacokinetic parameters were determined by non-compartmental analysis with nominal time and dose (Phoenix WinNonlin, Pharsight Corp, Mountain View, CA). PK parameters calculated using a non-compartmental analysis are summarized in Table 2 .

Table 1: PK parameter estimates from the NZW Rabbit PK Study

	Cmax (ug/mL)	**AUCall (day*ug/mL)**	**CL (mL/day)**	**Vss (mL)**
Vitreous	1030	5360	0.271	0.812
Aqueous	4.50	148	5.16	403
Serum	0.147	2.32	1260	19000

[584] RabFab vitreal PK following release from cross-linked HA RabFab in NZW Rabbits is consistent with predictions based on *in vitro* release. Initial higher concentrations are due to the dose solution containing ~3.6% Free Fab and ~4.9% Free Fab-HA species. Release half-life in rabbit vitreous fluid is estimated to be 53 days.

[585] The terminal half-life of free Fab in vitreous is equal to the half-life of the reversible prodrug linker. This means that once dynamics of drug release from HA and subsequent elimination from vitreous reach equilibrium, the effective elimination half-life of active drug in vitreous will be 53/3.2 = 16.5 times longer compared to that typically observed following an IVT injection of free Fab.

Example 5E Absence of Significant Fragmentation or particle movement in NHP eye.

[586] Two cynomolgus monkeys were administered bilaterally a single ITV administration of placebo cross-linked HA gel-Fluorescein (50 uL/eye) in the inferior temporal quadrant. The animals were observed for 30 days for clinical observations, body weight changes, food consumption and ocular observations (IOP, biomicroscopic (slit lamp) and funduscopic examinations. In addition the location and cohesiveness of the material was monitored over the same period using gonioscopy, gonioimaging, fundus imaging using a confocal scanning laser ophthalmoscope and fluorometry using a Fluoroton.

[587] Figure 13A is a representative cSLO image taken at day 15. The TA (arrow) remains in the inferior vitreous and does not obscure the fovea (F) or optic disc (ON). Figure 13B is an image taken at necropsy with cobalt blue light following removal of the anterior segment

and lens. Note the TA (arrow) remains cohesive. As can be seen, the placebo cross-linked HA gel **m2** showed minimal fragmentation and movement after 30 days.

Example 7F Cross-linked HA RabFab gel Tolerability Study in Rabbit

[588] Three New Zealand White rabbits were administered bilaterally a single ITV administration of cross-linked -HA-RabFab gel (50 µL/eye) in the inferior temporal quadrant. The animals were observed for 60 days for clinical observations, body weight changes, food consumption and ocular observations (IOP, biomicroscopic (slit lamp) and funduscopic examinations). Serum samples were taken for ADA and TK. At necropsy, the eyes were removed and processed for histopathology. Figure 14 shows a histology section. As can be seen, cross-linked -HA-RabFab gel was well tolerated in a 2-month study. No cellular infiltrate, no inflammatory reaction, and no foreign body reaction were observed (6 eyes).

Example 7G Cross-linked HA G6.31 AARR gel Tolerability Study in Cynomolgus Macaques

[589] Two cynomolgus macaques were administered bilaterally a single ITV injection of cross-linked HA gel conjugated to the anti-VEGF Fab, G6.31 AARR (50 µL/ eye; 1.92 mg Fab/ eye) in the inferior temporal quadrant. The animals were observed for 3 months (92 days) for clinical observations, body weight changes, food consumption, and ocular observations (IOP, biomicroscopic (slit lamp) and funduscopic examinations). The location and cohesiveness of the material was monitored over the same period using gonioscopy and gonioimaging. Serum samples were taken for ADA and TK assessment and eyes were assessed by histopathology at 3 months.

[590] The hydrogel remained cohesive and in the inferior vitreous throughout the period of assessment. No significant in-life inflammation was noted despite the induction of ADA in both animals by day 28. There were no test article related changes in clinical observation, qualitative food consumption, and body weights. Figure 15 shows a superoinferior histology section of the inferior calotte of the eye that contains the test article. As can be seen cross-linked-HA-G6.31 AARR gel was well tolerated in a 3-month study. No cellular infiltrate, no inflammatory reaction, and no foreign body reaction were observed (4 eyes).

[591] Compared to PEG-based particulate hydrogel conjugated to ranibizumab, cross-linked-HA-G6.31 AARR gel displays a superior safety profile. When injected into the inferior vitreous cavity, cross-linked-HA-G6.31 AARR gel does not move and remains below the visual axis and thus is not expected to interfere with patient vision. Conversely, PEG-based particulate hydrogels moved freely within the vitreous cavity.