reduce or eliminate the hyaluronic acid causing the vascular occlusion, thereby reducing or eliminating the risk of permanent damage to the eye.

[007] Aspects of the present specification disclose methods of reducing or eliminating a hyaluronic acid-induced blockage in one or more blood vessels supplying blood to an eye in an individual in need thereof. The disclosed methods comprise administering a composition comprising a hyaluronidase to an individual in a manner that reduces or eliminates a hyaluronic acid-induced blockage in one or more blood vessels supplying blood to an eye. In aspects, the disclosed methods administer composition comprising a hyaluronidase to a suprachoroidal space of an eye. In other aspects, the disclosed methods administer a composition comprising a hyaluronidase using a delivery system, such as, e.g., a needle and syringe, an ADG needle, or a microinjector. The disclosed methods can administer a composition comprising a hyaluronidase in a single- or multi-dose amount ranging from about 15 IU to about 10,000 IU of a hyaluronidase.

[008] Aspects of the present specification disclose methods of reducing or inhibiting a vascular occlusion in an eye of an individual in need thereof. The disclosed methods comprise administering a composition comprising a hyaluronidase to an individual in a manner that reduces or eliminates a hyaluronic acid-induced blockage in one or more blood vessels supplying blood to an eye, thereby reducing or inhibiting the vascular occlusion in the eye. In aspects, the disclosed methods administer composition comprising a hyaluronidase to a suprachoroidal space of an eye. In other aspects, the disclosed methods administer a composition comprising a hyaluronidase using a delivery system, such as, e.g., a needle and syringe, an ADG needle, or a microinjector. The disclosed methods can administer a composition comprising a hyaluronidase in a single- or multi-dose amount ranging from about 15 IU to about 10,000 IU of a hyaluronidase.

[009] Aspects of the present specification disclose methods of reducing or inhibiting hyaluronic acid-induced loss of vision in an individual in need thereof. The disclosed methods comprise administering a composition comprising a hyaluronidase to an individual in a manner that reduces or eliminates a hyaluronic acid-induced blockage in one or more blood vessels supplying blood to an eye, thereby reducing or inhibiting the hyaluronic acid-induced loss of vision in the individual. In aspects, the disclosed methods administer a composition comprising a hyaluronidase to a suprachoroidal space of an eye. In other aspects, the disclosed methods administer a composition comprising a hyaluronidase using a delivery system, such as, e.g., a needle and syringe, an ADG needle, or a microinjector. The disclosed methods can administer a composition comprising a hyaluronidase in a single- or multi-dose amount ranging from about 15 IU to about 10,000 IU of a hyaluronidase.

[010] Other aspects of the present specification disclose a delivery system, such as, e.g., a needle and syringe, an ADG needle, or a microinjector, comprising a composition comprising a hyaluronidase. In aspects, the disclosed delivery system delivers a composition comprising a hyaluronidase to a suprachoroidal space of an eye. The disclosed delivery system can administer a composition comprising

hyaluronidase can be administered to the same eye within 5 to 15 minutes. In yet other aspects of these embodiments, 7 to 15 doses of a composition comprising a hyaluronidase can be administered to the same eye within 5 to 15 minutes. In still other aspects of these embodiments, 8 to 12 doses of a composition comprising a hyaluronidase can be administered to the same eye within 5 to 15 minutes. In still other aspects of these embodiments, 10 doses of a composition comprising a hyaluronidase can be administered to the same eye within 5 to 15 minutes.

[057] In aspects of this embodiment, reducing or eliminating a hyaluronic acid-induced blockage in one or more blood vessels supplying blood to an eye restores or maintains one or more qualitative or quantitative aspects of vision by, e.g., at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90% or at least 100%. In other aspects of this embodiment, reducing or eliminating a hyaluronic acid-induced blockage in one or more blood vessels supplying blood to an eye restores or maintains one or more qualitative or quantitative aspects of vision by, e.g., at most 10%, at most 20%, at most 30%, at most 40%, at most 50%, at most 60%, at most 70%, at most 80%, at most 90% or at most 100%. In yet other aspects of this embodiment, reducing or eliminating a hyaluronic acid-induced blockage in one or more blood vessels supplying blood to an eye restores or maintains one or more qualitative or quantitative aspects of vision by, e.g., about 10% to about 100%, about 10% to about 90%, about 10% to about 80%, about 10% to about 70%, about 10% to about 60%, about 10% to about 50%, about 10% to about 40%, about 10% to about 30%, about 10% to about 20%, about 20% to about 100%, about 20% to about 90%, about 20% to about 80%, about 20% to about 70%, about 20% to about 60%, about 20% to about 50%, about 20% to about 40%, about 20% to about 30%, about 30% to about 100%, about 30% to about 90%, about 30% to about 80%, about 30% to about 70%, about 30% to about 60%, about 30% to about 50%, about 30% to about 40%, about 40% to about 100%, about 40% to about 90%, about 40% to about 80%, about 40% to about 70%, about 40% to about 60%, about 40% to about 50%, about 50% to about 100%, about 50% to about 90%, about 50% to about 80%, about 50% to about 70%, about 50% to about 60%, about 60% to about 100%, about 60% to about 90%, about 60% to about 80%, about 60% to about 70%, about 70% to about 100%, about 70% to about 90%, about 70% to about 80%, about 80% to about 100%, about 80% to about 90%, or about 90% to about 100%. In still other aspects of this embodiment, reducing or eliminating a hyaluronic acid-induced blockage in one or more blood vessels supplying blood to an eye restores or maintains one or more qualitative or quantitative aspects of vision for, e.g., at least one week, at least one month, at least two months, at least three months, at least four months, at least five months, at least six months, at least seven months, at least eight months, at least nine months, at least ten months, at least eleven months, or at least twelve months.

[058] In one embodiment, as shown in **FIGS. 6A-D**, composition comprising a hyaluronidase can be administered to the suprachoroidal space. Referring to **FIGS. 6A-B**, a delivery system, depicted as a microinjector, is positioned over a portion of the sclera with the device perpendicular to the surface of the injection site. Referring now to **FIG. 6C**, the device is then pressed against the scleral surface to create a “dimple” around the hub of the delivery system. As shown in **FIG. 6D**, the needle of the delivery system is then inserted through the scleral layer and into the suprachoroidal space, and the plunger of the device is depressed gently while maintaining the dimple on the eye surface for 3-5 seconds to completely administer

1 minute to about 7 minutes, about 1 minute to about 10 minutes, about 1 minute to about 15 minutes, about 3 minutes to about 5 minutes, about 3 minutes to about 7 minutes, about 3 minutes to about 10 minutes, about 3 minutes to about 15 minutes, about 5 minutes to about 7 minutes, about 5 minutes to about 10 minutes, about 5 minutes to about 15 minutes, about 5 minutes to about 30 minutes, about 10 minutes to about 15 minutes, about 10 minutes to about 30 minutes, about 15 minutes to about 30 minutes, about 15 minutes to about 45 minutes, about 15 minutes to about 60 minutes, about 15 minutes to about 75 minutes, about 15 minutes to about 90 minutes.

26. A kit comprising one or more containers, each container including a pharmaceutical composition including a hyaluronidase.
27. The kit according to embodiment 26, wherein the pharmaceutical composition is in a liquid formulation.
28. The kit according to embodiment 26, wherein the pharmaceutical composition is in a dried formulation.
29. The kit according to any one of embodiments 26-28, wherein the one or more containers are each a delivery system.
30. The kit according to any one of embodiments 26-28, further comprising a delivery system.
31. The kit according to any one of embodiments 26-30, further comprising another container including a solvent.
32. The kit according to any one of embodiments 26-31, further comprising instructions.

EXAMPLES

[070] The following non-limiting examples are provided for illustrative purposes only in order to facilitate a more complete understanding of representative embodiments now contemplated. These examples should not be construed to limit any of the embodiments described in the present specification, including those pertaining to the compounds, pharmaceutical compositions, or methods and uses disclosed herein.

Example 1
Rabbit Model of Filler-Induced Vascular Occlusion

[071] In this example, New Zealand white rabbits were used to simulate hyaluronic acid polymer associated vascular occlusive loss of vision. These animals were selected due to the similarity of their ocular vascular anatomy to that of humans.

[072] New Zealand white rabbits weighing 2.0 to 3.0 kg were acclimated to the study environment for a minimum of 1 week prior to the beginning of the study. At the completion of the acclimation period, each animal was physically examined for determination of suitability for the study including examination of the skin and external ears, eyes, abdomen, neurological, behavior, and general body condition. Animals determined to be in good health were released to the study. Released animals were allocated to four group of 3 animals each with each animal uniquely identified by a cage card number.

[073] On the day of the surgical procedure (Day 0), all animals were anesthetized and dosed with an antibiotic. Each animal then underwent a surgical procedure to expose the right carotid artery

hyaluronic acid polymers can occlude blood flow to the retina and cause loss of retinal function and serve as a good model for hyaluronic acid polymer associated vascular occlusive loss of vision.

Table 1. Assessment of Blood Flow in Retina by OCT-A Analysis

Animal	Pre-induction Day 0		Post-induction Day 3	
	Left Eye	Right Eye	Left Eye	Right Eye
Group 1-1	+++	+++	+++	–
Group 1-2	+++	+++	+++	–
Group 1-3	+++	+++	+++	–
Group 2-1	+++	+++	+++	–
Group 2-2	+++	+++	+++	–
Group 2-3	+++	+++	+++	–
Group 3-1	+++	+++	+++	+++
Group 3-2	+++	+++	+++	+
Group 3-3	+++	+++	+++	++
Group 3-4	+++	+++	+++	+

+++ Normal blood flow measured in retina.
++ Near-normal blood flow measured in retina.
+ Low but significant blood flow measured in retina.
– No appreciable blood flow measured in retina.

Table 2. Assessment of Neuronal Activity in Retina by ERG Analysis

Animal	Pre-induction Day 0		Post-induction Day 3	
	Left Eye	Right Eye	Left Eye	Right Eye
Group 1-1	+++	+++	+++	–
Group 1-2	+++	+++	+++	–
Group 1-3	+++	+++	+++	–
Group 2-1	+++	+++	+++	–
Group 2-2	+++	+++	+++	–
Group 2-3	+++	+++	+++	–
Group 3-1	+++	+++	+++	+++
Group 3-2	+++	+++	+++	+
Group 3-3	+++	+++	+++	++
Group 3-4	+++	+++	+++	+

+++ Normal neuronal activity measured in retina.
++ Near-normal neuronal activity measured in retina.
+ Low but significant neuronal activity measured in retina.
– No appreciable neuronal activity measured in retina.

[076] Analysis of Group 3 animals demonstrated that administration of hyaluronidase reversed hyaluronic acid polymer associated vascular occlusion in the retina. At pre-induction Day 0, the right eye of Group 3 animals exhibited normal blood flow to the retina based on OCT-A analysis (Table 1) as well as normal neuronal activity in the retina based on ERG readings (Table 2). These baseline measurements show that the animals in Group 3 exhibited functional neuronal activity. Surprisingly, post-induction Day 3, all animals also showed significant blood flow and neuronal activity in the retina (Tables 1 and 2). Although these levels were distinguishable from measurements obtained from the right eye on pre-induction Day 0 as well as measurements from the left eye control, the activity measured nonetheless illustrated a significant recovery from the vascular occlusion caused by the presence of hyaluronic acid polymers. These results demonstrate that hyaluronic acid polymers can occlude blood flow to the retina and cause loss of retinal function and serve as a good model for hyaluronic acid polymer associated vascular occlusive loss of vision. Furthermore, remarkably, small volumes of hyaluronidase administration into the suprachoroidal space

cleared the hyaluronic acid dermal filler occlusion within the retinal circulation allowing for the reperfusion of the retinal tissue and reestablishment of neuronal activity.

Example 2

Rabbit Model of Filler-Induced Vascular Occlusion

[077] New Zealand white rabbits will be used to simulate hyaluronic acid associated vascular occlusive loss of vision. These animals will be selected due to the similarity of their ocular vascular anatomy to that of humans. New Zealand white rabbits weighing 2.0 to 3.0 kg will be divided into groups based on the hyaluronidase dose and administration time.

[078] Hyaluronic acid filler will be administered into the internal carotid artery of animals to create a central retinal artery occlusion. This artery occlusion as well as subsequent ischemia will be confirmed by both retinal fundus photography, OCT-A, and ERG analyses. Different doses of hyaluronidase will be suprachoroidally administered at several post-obstruction time points to assess both dose and timing effectiveness of the treatment. Control animals will be injected with hyaluronic acid filler in the same manner as experimental animals but will receive no hyaluronidase treatment. Fundus photography and electroretinogram changes will be recorded at 30, 60, 90, and 120 minutes after administration of hyaluronidase. Electroretinography will be performed after 60 and 120 minutes to confirm the retinal reperfusion and electrophysiologic function.

[079] In one series of experiments, a central retinal artery occlusion will be induced by injecting 0.5 mL to 0.9 mL of hyaluronic acid filler into rabbits, which will be divided into four experimental groups each containing 2 or 3 animals with Group 1 animals receiving suprachoroidally administered 100 µL hyaluronidase (400 IU/mL) 5 minutes after hyaluronic acid filler injection; Group 2 animals receiving suprachoroidally administered 100 µL hyaluronidase (400 IU/mL) 10 minutes after hyaluronic acid filler injection; Group 3 animals receiving suprachoroidally administered 100 µL hyaluronidase (600 IU/mL) 5 minutes after hyaluronic acid filler injection; and Group 4 animals receiving suprachoroidally administered 100 µL hyaluronidase (650 IU/mL) 10 minutes after hyaluronic acid filler injection.

[080] In another series of experiments, a central retinal artery occlusion will be induced by injecting 0.5 mL to 0.9 mL of hyaluronic acid filler into rabbits, which will be divided into four experimental groups each containing 2 or 3 animals with Group 1 animals receiving suprachoroidally administered 100 µL hyaluronidase (1,000 IU/mL) 5 minutes after hyaluronic acid filler injection; Group 2 animals receiving suprachoroidally administered 100 µL hyaluronidase (1,000 IU/mL) 10 minutes after hyaluronic acid filler injection; Group 3 animals receiving suprachoroidally administered 100 µL hyaluronidase (3,000 IU/mL) 5 minutes after hyaluronic acid filler injection; and Group 4 animals receiving suprachoroidally administered 100 µL hyaluronidase (3,000 IU/mL) 10 minutes after hyaluronic acid filler injection.

[081] In another series of experiments, a central retinal artery occlusion will be induced by injecting 0.5 mL to 0.9 mL of hyaluronic acid filler into rabbits, which will be divided into four experimental groups each