OBJECTS AND SUMMARY OF THE ~~INVENTION~~DISCLOSURE

[00014a] In an aspect, there is provided a sustained release biodegradable ocular implant comprising a hydrogel and 150 µg to 800 µg of axitinib, wherein the hydrogel comprises a polymer network comprising polyethylene glycol (PEG) units, wherein axitinib particles are dispersed within the hydrogel, and wherein the implant is cylindrical and in its dry state has a diameter of 0.1 mm to 0.5 mm and a length of less than 17 mm.

[00014b] In another aspect, there is provided a sustained release biodegradable ocular implant as defined above for use in treating neovascular age-related macular degeneration (AMD) in a patient in need thereof.

[00014c] In another aspect, there is provided a method of manufacturing the sustained release biodegradable ocular implant as defined above, the method comprising the steps of forming a hydrogel by mixing and reacting an electrophilic group-containing multi-arm PEG precursor with a nucleophilic group-containing multi-arm PEG precursor or another nucleophilic group-containing crosslinking agent in a buffered solution in the presence of axitinib particles, allowing the mixture to gel to form the hydrogel, and drying the hydrogel.

[00014d] In another aspect, there is provided a kit comprising one or more sustained release biodegradable ocular implant(s) as defined above and one or more needles for injection.

[00015] It is an object of certain ~~embodiments~~ examples of the present ~~invention~~ disclosure to provide an ocular implant comprising a tyrosine kinase inhibitor (TKI) such as axitinib that is effective for treating ocular diseases such as neovascular age-related macular degeneration (AMD), DME, and RVO in a patient for an extended period of time.

[00016] Another object of certain examples~~embodiments~~ of the present ~~invention~~ disclosure is to provide an ocular implant comprising a tyrosine kinase inhibitor (TKI) such as axitinib that provides for sustained release of the TKI into the eye.

[00017] Another object of certain examples~~embodiments~~ of the present ~~invention~~ disclosure is to provide an ocular implant comprising a TKI such as axitinib that is pre-loaded into a syringe, thereby avoiding contamination of the implant prior to injection as no further preparation steps are needed.

[00018] Another object of certain examples~~embodiments~~ of the present ~~invention~~ disclosure is to provide an ocular implant comprising a TKI such as axitinib that is sufficiently biodegradable, i.e., cleared from the eye within a time coinciding with TKI release, avoiding floaters within the patient's eye (empty implant vehicle residues) and/or avoiding the need for removal of the empty implant from the eye after the treatment period.

[00019] Another object of certain examples~~embodiments~~ of the present ~~invention~~ disclosure is to provide an ocular implant comprising a TKI such as axitinib that is biodegradable, wherein decomposition of the implant into smaller particles that may e.g. impact vision are avoided during implant degradation.

[00020] Another object of certain examples~~embodiments~~ of the present disclosure~~invention~~ is to provide an ocular implant comprising a TKI such as axitinib, wherein the stability of the ocular implant is less affected by varying environments in the eye such as vitreous humor viscosity, pH of the vitreous humor, composition of the vitreous humor and/or intraocular pressure (IOP) when compared to hydrogels formed *in situ* after injection.

[00021] Another object of certain examples~~embodiments~~ of the present disclosure~~invention~~ is to provide an ocular implant comprising a TKI such as axitinib that is biocompatible and non-immunogenic due to the implant being free or substantially free of animal- or human-derived components.

[00022] Another object of certain examples~~embodiments~~ of the present disclosure~~invention~~ is to provide an ocular implant comprising a TKI such as axitinib that is free of preservatives, such as antimicrobial preservatives.

[00023] Another object of certain examples~~embodiments~~ of the present disclosure~~invention~~ is to provide an ocular implant comprising a TKI such as axitinib that is easy to inject, in particular intravitreally.

[00024] Another object of certain examples~~embodiments~~ of the present disclosure~~invention~~ is to provide an ocular implant comprising a TKI such as axitinib that contains a therapeutically effective amount of said TKI but is relatively small in length and/or diameter.

[00025] Another object of certain examples~~embodiments~~ of the present disclosure~~invention~~ is to provide an ocular implant comprising a TKI such as axitinib that is dimensionally stable when in a dry state but changes its dimensions upon hydration, e.g. after administration to the eye.

[00026] Another object of certain examples~~embodiments~~ of the present disclosure~~invention~~ is to provide an ocular implant comprising a TKI such as axitinib that has a small diameter when in a dry state to fit into the lumen of a fine-

diameter needle (such as a 22- to 30-gauge needle) and increases in diameter but decreases in length upon hydration, e.g. after administration to the eye; thus, providing a minimally invasive method of administration.

[00027] Another object of certain examples~~embodiments~~ of the present disclosure~~invention~~ is to provide an ocular implant comprising a TKI such as axitinib that is injected in a dry form and hydrates *in situ* (i.e. in the eye) when injected.

[00028] Another object of certain examples~~embodiments~~ of the present disclosure~~invention~~ is to provide an ocular implant comprising a TKI such as axitinib that when placed in the eye has low TKI concentration at the implant surface thereby avoiding toxicity of the TKI when the implant gets in contact with ocular cells or tissues such as the retina.

[00029] Another object of certain examples~~embodiments~~ of the present disclosure~~invention~~ is to provide an ocular implant comprising a TKI such as axitinib that is stable and has a defined shape and surface area both in a dry state prior to as well as in a hydrated state after the injection (i.e. inside the eye).

[00030] Another object of certain examples~~embodiments~~ of the present disclosure~~invention~~ is to provide an ocular implant comprising a TKI such as axitinib that is easy to handle, in particular that does not spill or fragment easily.

[00031] Another object of certain examples~~embodiments~~ of the present disclosure~~invention~~ is to provide an ocular implant comprising a TKI such as axitinib that enables administration of an exact dose (within a broad dose range), thereby avoiding the risk of over- and under-dosing.

[00032] Another object of certain examples~~embodiments~~ of the present disclosure~~invention~~ is to provide an ocular implant comprising a TKI such as axitinib that generally stays in the area of the eye to which it was administered.

[00033] Another object of certain examples~~embodiments~~ of the present disclosure~~invention~~ is to provide an ocular implant comprising a TKI such as axitinib, wherein the implant causes minimal or no visual impairment after administration.

[00034] Another object of certain examples~~embodiments~~ of the present disclosure~~invention~~ is to provide an ocular implant comprising a TKI such as axitinib that is safe and well tolerated.

[00035] Another object of certain examples~~embodiments~~ of the present disclosure ~~invention~~ is to provide an ocular implant comprising a TKI such as axitinib that does not induce severe adverse events, such as severe ocular adverse events.

[00036] Another object of certain examples~~embodiments~~ of the present disclosure~~invention~~ is to provide an ocular implant comprising a TKI such as axitinib that provides for sustained release of a therapeutically effective amount of the TKI such as axitinib over an extended period of time, such as over a period of up to 3 months or longer, such as at least 6, at least 9, at least 11 months, or at least 13 months.

[00037] Another object of certain examples~~embodiments~~ of the present disclosure~~invention~~ is to provide an ocular implant comprising a TKI such as axitinib that provides for sustained release of a TKI such as axitinib over an extended period of time, such as over a period of up to 3 months or longer, such as at least 6, at least 9, at least 11 months, or at least 13 months, thereby avoiding the need for frequent implant administrations.

[00038] Another object of certain examples~~embodiments~~ of the present disclosure~~invention~~ is to provide an ocular implant comprising a TKI such as axitinib that provides for sustained release of the TKI such as axitinib over an extended period of time, such as over a period of up to 3 months or longer, such as at least 6, at least 9, at least 11 months, or at least 13 months, thereby inhibiting angiogenesis over this period of time.

[00039] Another object of certain examples~~embodiments~~ of the present disclosure~~invention~~ is to provide an ocular implant comprising a TKI such as axitinib that provides for sustained release of the TKI over an extended

period of time, such as over a period of up to 3 months or longer, such as at least 6, at least 9, at least 11 months, or at least 13 months, wherein the TKI levels in ocular tissues such as the retina and the choroid, as well as the vitreous humor are

consistently maintained at a therapeutically efficient level, in particular at a level sufficient for inhibition of angiogenesis, over this period of time.

[00040] Another object of certain examples~~embodiments~~ of the present disclosure~~invention~~ is to provide an ocular implant comprising a TKI such as axitinib that provides for sustained release of a TKI such as axitinib over an extended period of time, such as over a period of up to 3 months or longer, such as at least 6, at least 9, at least 11 months, or at least 13 months, wherein no toxic concentrations of the TKI are observed in ocular tissues such as the retina and the choroid, as well as the vitreous humor over this period of time.

[00041] Another object of certain examples~~embodiments~~ of the present disclosure~~invention~~ is to provide an ocular implant comprising a TKI such as axitinib that provides for sustained release of a TKI such as axitinib over an extended period of time, such as over a period of up to 3 months or longer, such as at least 6, at least 9, at least 11 months, or at least 13 months, wherein the TKI is not accumulating in the anterior chamber of the eye.

[00042] Another object of certain examples~~embodiments~~ of the present disclosure~~invention~~ is to provide an ocular implant comprising a TKI such as axitinib that provides sustained release of a TKI over an extended period of time, such as over a period of up to 3 months or longer, such as at least 6, at least 9, at least 11 months, or at least 13 months, wherein the TKI is not or is not substantially resorbed systemically thereby substantially avoiding systemic toxicity.

[00043] Another object of certain examples~~embodiments~~ of the present disclosure~~invention~~ is to provide a method of treating ocular diseases such as AMD, DME, and RVO in a patient in need thereof, for a treatment period of up to 3 months or longer, such as at least 6, at least 9, at least 11 months, or at least 13 months.

[00044] Another object of certain examples~~embodiments~~ of the present disclosure~~invention~~ is to provide a method of treating ocular diseases such as AMD, DME, and RVO in a patient in need thereof, for a treatment period of up to 3 months or longer, such as at least 6, at least 9, at least 11 months, or at least 13 months, without the need for the administration of rescue medication during the treatment period, or wherein rescue medication is required to be administered only rarely, such as 1, 2 or 3 times, during the treatment period.

[00045] Another object of certain examples~~embodiments~~ of the present disclosure~~invention~~ is to provide a method of treating ocular diseases such as AMD, DME, and RVO in a patient in need thereof, such as a patient who has been treated with anti-VEGF before or a patient who is naïve for anti-VEGF treatment.

[00046] Another object of certain examples~~embodiments~~ of the present disclosure~~invention~~ is to provide a method of treating ocular diseases such as AMD, DME, and RVO in a patient in need thereof, such as a patient who has been treated with anti-VEGF before and has not responded to the previous anti-VEGF treatment.

[00047] Another object of certain examples~~embodiments~~ of the present disclosure~~invention~~ is to provide a method of treating ocular diseases such as AMD, DME, and RVO in a patient in need thereof, such as a patient with a diagnosis of primary subfoveal neovascularization (SFNV) secondary to AMD.

[00048] Another object of certain examples~~embodiments~~ of the present disclosure~~invention~~ is to provide a method of treating ocular diseases such as AMD, DME, and RVO in a patient in need thereof, such as a patient with a diagnosis of previously treated subfoveal neovascularization (SFNV) secondary to neovascular AMD with leakage involving the fovea, who has been previously treated with anti-VEGF.

[00049] Another object of certain examples~~embodiments~~ of the present disclosure~~invention~~ is to provide a method of manufacturing an ocular implant comprising a TKI such as axitinib.

[00050] Another object of certain examples~~embodiments~~ of the present disclosure~~invention~~ is to provide a method of protecting an ocular implant from premature hydration during storage and handling, wherein the ocular implant is sensitive to moisture such that it for instance changes its dimensions upon hydration.

[00051] Another object of certain examples~~embodiments~~ of the present disclosure~~invention~~ is to provide a method of minimizing potential tissue damage during injection of an ocular implant.

[00052] Another object of certain examples~~embodiments~~ of the present disclosure~~invention~~ is to provide a kit comprising one or more ocular implants comprising a TKI such as axitinib and optionally comprising a means for injecting the ocular implant.

[00053] Another object of certain examples~~embodiments~~ of the present disclosure~~invention~~ is to provide a method of reducing the central subfield thickness as measured by optical coherence tomography in a patient whose central subfield thickness is elevated due to an ocular disease involving angiogenesis by for instance reducing retinal fluid.

[00054] Another object of the present disclosure~~invention~~ is to provide a method of essentially maintaining or preventing a clinically significant increase of the central subfield thickness as measured by optical coherence tomography in a patient whose central subfield thickness is elevated due to an ocular disease involving angiogenesis while not increasing retinal fluid.

[00055] Another object of certain examples~~embodiments~~ of the present disclosure~~invention~~ is to provide a method of reducing, essentially maintaining or preventing a clinically significant increase of the central subfield thickness as measured by optical coherence tomography in a patient whose central subfield thickness is elevated due to an ocular disease involving angiogenesis while improving or at least not impairing the patient's visual acuity as measured for instance by means of best corrected visual acuity.

[00056] Another object of certain examples~~embodiments~~ of the present disclosure~~invention~~ is to provide a method of improving the vision of a patient whose vision is impaired due to an ocular disease involving angiogenesis.

[00057] Another object of certain examples~~embodiments~~ the present disclosure~~invention~~ is to provide a method of improving the vision of a patient whose vision is impaired due to the presence of retinal fluid (caused for instance by an ocular disease involving angiogenesis) by means of reducing retinal fluid in the patient (as for instance evidenced by a reduction the central subfield thickness as measured by optical coherence tomography).

[00058] One or more of these objects of the present disclosure~~invention~~ and others are solved by one or more examples~~embodiments~~ as disclosed and claimed herein.

[00059] The individual examples~~aspects~~ of the present disclosure~~invention~~ are disclosed in the specification and claimed in the independent claims, while the dependent claims claim particular examples~~embodiments~~ and variations of these examples~~aspects~~ of the disclosure~~invention~~. Details of the various examples~~aspects~~ of the present disclosure~~invention~~ are provided in the detailed description below.

[00060] Throughout this application various references are cited. The disclosures of these references are hereby incorporated by reference into the present disclosure. In case of conflict, the disclosure in the present application prevails.

BRIEF DESCRIPTION OF THE DRAWINGS

[00061] **Figure 1** Schematic representation of one embodiment of the implant packaging. In this embodiment, implants are pre-loaded into thin-walled needles separately packaged from the injection device. An all-in-one device with needles already connected to the injection device is also possible.

CLAIMS

1. A sustained release biodegradable ocular implant comprising a hydrogel and ~~at least about~~ 150 µg to 800 µg of ~~a tyrosine kinase inhibitor (TKI)~~axitinib, wherein the hydrogel comprises a polymer network comprising polyethylene glycol (PEG) units, wherein ~~TKI~~ axitinib particles are dispersed within the hydrogel, and wherein the implant is cylindrical and in its dry state has a diameter of 0.1 mm to 0.5 mm and a length of less than ~~about~~ 17 mm.

~~2. The sustained release biodegradable ocular implant of claim 1, wherein the implant is cylindrical and in its dry state has a diameter of about 0.1 mm to about 0.5 mm.~~

~~3. The sustained release biodegradable ocular implant of claim 1, wherein the implant is non-cylindrical.~~

~~4. The sustained release biodegradable ocular implant of any of claims 1 to 3, wherein the TKI is axitinib.~~

~~5~~2. The sustained release biodegradable ocular implant of claim ~~4~~1, wherein the implant comprises axitinib in an amount of ~~about 150 µg to about 1800 µg, preferably in an amount of about 150 µg to about 1200 µg, more preferably in an amount of about~~ 480 µg to ~~about~~ 750 µg or 320 µg to 500 µg or ~~of about~~ 160 µg to ~~about~~ 250 µg.

3. The sustained release biodegradable ocular implant of claim 2, wherein the implant comprises axitinib in an amount of 200 µg, 400 µg, or 600 µg.

~~6~~4. The sustained release biodegradable ocular implant of any of the preceding claims, wherein the implant in its dry state has a total weight of ~~about~~ 0.2 mg to ~~about~~ 1.5 mg, preferably a total weight of ~~about~~ 0.75 mg to 1.25 mg.

~~7. The sustained release biodegradable ocular implant of any of the preceding claims, wherein the implant is for administration into the posterior section of the eye.~~

~~8. The sustained release biodegradable ocular implant of any of the preceding claims, wherein the implant is an intravitreal implant.~~

~~9. The sustained release biodegradable ocular implant of any of the preceding claims wherein the implant is cylindrical and in its dry state has a length of about 6 mm to about 10 mm.~~

~~10. The sustained release biodegradable ocular implant of any of the preceding claims wherein the implant is cylindrical and in its dry state has a diameter of about 0.2 mm to about 0.4 mm.~~

~~11~~5. The sustained release biodegradable ocular implant of any of the preceding claims, wherein the implant is cylindrical and in its hydrated state (after 24 hours in phosphate-buffered saline at a pH of 7.2 at 37 °C) has a length of equal to or less than ~~about~~ 10 mm and a diameter of equal to or less than ~~about~~ 0.8 mm.

~~12~~6. ~~The~~ The sustained release biodegradable ocular implant of any of the preceding claims, wherein the implant is cylindrical and has a ratio of the diameter in the hydrated state to the diameter in the dry state of less than ~~about~~ 5, preferably less than ~~about~~ 2.25~~.~~

~~13. The sustained release biodegradable ocular implant of any of the preceding claims, wherein the implant is cylindrical and,~~ and/or has a ratio of the length in the dry state to the length in the hydrated state of greater than ~~about~~ 0.7, preferably greater than ~~about~~ 0.8.

~~14~~7. The sustained release biodegradable ocular implant of any of the preceding claims, wherein the ~~TKI is axitinib and the~~ implant provides for the release of axitinib at an average rate of ~~about~~ 0.25 µg to ~~about~~ 2.5 µg per day, preferably of ~~about~~ 0.25 µg to ~~about~~ 1.5 µg per day, more preferably of ~~about~~ 0.3 µg to ~~about~~ 0.5 µg per day, in phosphate-buffered saline at a pH of 7.2 and 37 °C for a period of 30 days under non-sink simulated physiological conditions.

8. The sustained release biodegradable ocular implant of any of the preceding claims, wherein the implant is an intravitreal implant.

~~15~~9. The sustained release biodegradable ocular implant of any of the preceding claims, wherein the implant provides for the release of ~~the TKI~~ axitinib for a period of at least 3 months after administration, ~~or a period of~~ at least 6 months after administration, ~~or a period of~~ at least 9 months after administration, or ~~a period of~~ at least 12 months after administration~~., or a period of about 6 months to about 9 months after administration.~~

10. The sustained release biodegradable ocular implant of claim 9, wherein the implant provides for the release of axitinib for a period of 6 to 9 months after administration.

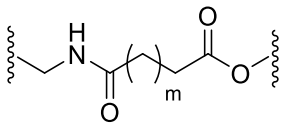
~~16. The sustained release biodegradable ocular implant of any of the preceding claims, wherein the implant biodegrades within about 2 to about 15 months, preferably within about 4 to about 13 months, or within about 9 to about 12 months, after administration to the vitreous humor.~~

~~17. The sustained release biodegradable ocular implant of any of the preceding claims, wherein the hydrogel comprises a polymer network comprising one or more units of polyalkylene glycol, polyethylene glycol, polyethylene oxide, polypropylene oxide, polyvinyl alcohol, poly (vinylpyrrolidinone), polylactic acid, polylactic-co-glycolic acid, random or block copolymers or combinations or mixtures of any of these, or one or more units of polyaminoacids, glycosaminoglycans, polysaccharides, or proteins.~~

~~18. The sustained release biodegradable ocular implant of claim 17, wherein the hydrogel comprises polyethylene glycol (PEG) units.~~

~~19~~11. The sustained release biodegradable ocular implant of ~~claim 18~~any of the preceding claims, wherein the hydrogel comprises multi-arm PEG units that are the same or different, and that have a number average molecular weight of from ~~about~~ 10,000 to ~~about~~ 60,000 Daltons, preferably ~~about~~ 20,000 Daltons.

~~20~~12. The sustained release biodegradable ocular implant of claim ~~18 or 19~~11, wherein the hydrogel comprises crosslinked PEG units and the crosslinks between the PEG units include a group represented by the following formula



wherein m is an integer from 0 to 10~~, preferably wherein m is 6~~.

13. The sustained release biodegradable ocular implant of claim 12, wherein m is 6.

~~21~~14. The sustained release biodegradable ocular implant of any of claims ~~18~~ 11 to ~~20~~13, wherein the PEG units comprise 4-arm and/or 8-arm PEG units~~, preferably 4a20k and 8a20k PEG units~~.

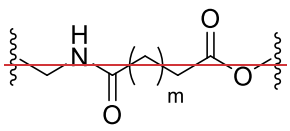
~~22. The sustained release biodegradable ocular implant of any of the preceding claims, wherein the implant in its wet state contains no more than about 40% by weight TKI of the wet composition.~~

~~23. The sustained release biodegradable ocular implant of any of the preceding claims, wherein the implant in its dry state contains from about 25% to about 75% by weight TKI and from about 20% to about 60% by weight PEG units (dry composition).~~

~~24. The sustained release biodegradable ocular implant of claim 23, wherein the implant in its dry state contains from about 60% to about 75% by weight TKI and from about 21% to about 31% by weight PEG units, or contains from about 45% to about 55% by weight TKI and from about 37% to about 47% by weight PEG units (dry composition).~~

~~25. The sustained release biodegradable ocular implant of any of the preceding claims, wherein the implant in its dry state contains from about 200 µg to about 1000 µg TKI per mm^3, and preferably contains from about 500 µg to about 800 µg axitinib per mm^3.~~

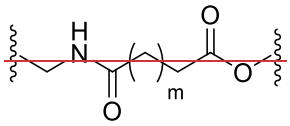
~~26. The sustained release biodegradable ocular implant of claim 1, wherein the implant is an intravitreal implant and comprises from about 480 µg to about 750 µg axitinib, preferably from about 540 µg to about 660 µg axitinib, more preferably about 600 µg axitinib, is cylindrical and has in its dry state a length of less than or equal to 10 mm and a diameter of about 0.3 mm to about 0.4 mm, and in its hydrated state (after 24 hours in phosphate-buffered saline at a pH of 7.2 at 37 °C) has a length of from about 6 mm to about 10.5 mm and a diameter of from about 0.6 mm to about 0.8 mm, and wherein the hydrogel comprises crosslinked 4a20k and 8a20k PEG units, wherein the crosslinks between the PEG units include a group represented by the following formula~~



~~wherein m is 6.~~

~~27. The sustained release biodegradable ocular implant of claim 1, wherein the implant is an intravitreal implant and comprises from about 160 µg to about 250 µg axitinib, preferably from about 180 µg to about 220 µg axitinib, more~~

~~preferably about 200 µg axitinib, is cylindrical and has in its dry state a length of less than about 17 mm and a diameter of about 0.2 mm to about 0.3 mm, and in its hydrated state (after 24 hours in phosphate-buffered saline at a pH of 7.2 at 37 °C) has a length of from about 6.5 mm to about 8 mm and a diameter of from about 0.7 mm to about 0.8 mm, and wherein the hydrogel comprises crosslinked 4a20k and 8a20k PEG units, wherein the crosslinks between the PEG units include a group represented by the following formula~~



~~wherein m is 6.~~

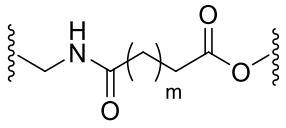
~~28~~15. The sustained release biodegradable ocular implant of any of the preceding claims, wherein the ~~TKI~~ axitinib particles have a d90 particle size of less than ~~about~~ 30 µm as determined by laser diffraction.

~~29~~16. The sustained release biodegradable ocular implant of any of the preceding claims, wherein the implant is free or substantially free of antimicrobial preservatives.

17. The sustained release biodegradable ocular implant of any of the preceding claims, wherein the implant in its dry state contains from 500 µg to 800 µg axitinib per mm^3.

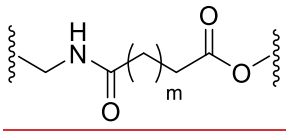
18. The sustained release biodegradable ocular implant of any of the preceding claims, wherein the implant in its dry state contains from 60% to 75% by weight axitinib and from 21% to 31% by weight PEG units, or contains from 45% to 55% by weight axitinib and from 37% to 47% by weight PEG units (dry composition).

19. The sustained release biodegradable ocular implant of claim 1, wherein the implant is an intravitreal implant and comprises from 480 µg to 750 µg axitinib, is cylindrical and has in its dry state a length of less than or equal to 10 mm and a diameter of 0.3 mm to 0.4 mm, and in its hydrated state (after 24 hours in phosphate-buffered saline at a pH of 7.2 at 37 °C) has a length of from 6 mm to 10.5 mm and a diameter of from 0.6 mm to 0.8 mm, and wherein the hydrogel comprises crosslinked 4a20k and 8a20k PEG units, wherein the crosslinks between the PEG units include a group represented by the following formula



wherein m is 6.

20. The sustained release biodegradable ocular implant of claim 1, wherein the implant is an intravitreal implant and comprises from 160 µg to 250 µg axitinib, is cylindrical and has in its dry state a length of less than 17 mm and a diameter of 0.2 mm to about 0.3 mm, and in its hydrated state (after 24 hours in phosphate-buffered saline at a pH of 7.2 at 37 °C) has a length of from 6.5 mm to 8 mm and a diameter of from 0.7 mm to 0.8 mm, and wherein the hydrogel comprises crosslinked 4a20k and 8a20k PEG units, wherein the crosslinks between the PEG units include a group represented by the following formula



wherein m is 6.

21. A sustained release biodegradable ocular implant according to any of the preceding claims for use in treating neovascular age-related macular degeneration (AMD) in a patient in need thereof.

~~30. A method of treating an ocular disease in a patient in need thereof, the method comprising administering to the patient a sustained release biodegradable ocular implant comprising a hydrogel and at least about 150 µg of a tyrosine kinase inhibitor (TKI), wherein TKI particles are dispersed within the hydrogel.~~

~~31. The method of claim 30, wherein the sustained release biodegradable ocular implant is according to any of claims 1 to 29.~~

~~32. The method of claim 30 or 31, wherein the implant is administered by injection into the vitreous humor.~~

~~33~~22. The sustained release biodegradable ocular implant of claim 21 for use in treating AMD ~~The method of any of claims 30 to 32, wherein the implant is administered once~~ during a treatment period of at least 3 months, or at least 6 months, or at least 9 months, or at least 12 months.

~~34~~23. The sustained release biodegradable ocular implant of claim 22~~The method of claim 33~~, wherein the treatment period is ~~about~~ 6 to ~~about~~ 9 months.

~~35~~24. The sustained release biodegradable ocular implant for use in treating AMD of claim 23~~The method of claim 33 or 34~~, wherein the implant is an intravitreal implant, wherein the~~TKI is axitinib and the axitinib~~ dose administered per eye ~~administered~~ once during the treatment period is from ~~about~~ 150 µg to ~~about~~ 1800 µg, preferably from ~~about~~ 150 µg to 1200 µg, more preferably from 480 µg to 750 µg axitinib and ~~wherein the dose~~ is contained in one ~~implant or in two, three~~ or more implant(s) administered concurrently.

~~36. The method of claim 35, wherein the axitinib dose is from about 160 µg to about 250 µg, preferably about 200 µg.~~

~~37. The method of claim 35, wherein the axitinib dose is from about 480 µg to about 750 µg, preferably about 600 µg.~~

~~38. The method of any of claims 30 to 37, wherein the ocular disease is a retinal disease.~~

~~39. The method of claim 38, wherein the disease is retinal vein occlusion (RVO), diabetic macular edema (DME), or neovascular age-related macular degeneration (AMD).~~

~~40. The method of claim 39, wherein the disease is AMD.~~

~~41. The method of any of claims 30 to 40, wherein the treatment is effective in reducing, essentially maintaining or preventing a clinically significant increase of the central subfield thickness as measured by optical coherence tomography in a patient whose central subfield thickness is elevated.~~

~~42~~25. The sustained release biodegradable ocular implant for use in treating AMD of any of claims 21 to 24~~The method of any of claims 30 to 41~~, wherein concurrently or in combination with the treatment with the ~~sustained release ocular~~ implant an anti-VEGF agent is administered to the patient.

26. The sustained release biodegradable ocular implant for use in treating AMD of any of claims 21 to 25, wherein the treatment is effective in reducing, essentially maintaining or preventing a clinically significant increase in the central subfield thickness as measured by optical coherence tomography in a patient whose central subfield thickness is elevated due to a retinal disease involving angiogenesis.

~~43. The method of any of claims 30 to 41, wherein an anti-VEGF agent is administered in combination with the implant, and is administered within about 1, about 2 or about 3 months from the administration of the implant.~~

~~44. The method of claim 42 or 43, wherein the anti-VEGF agent is selected from the group consisting of aflibercept, bevacizumab, pegaptanib, ranibizumab, and brolucizumab and is administered by intravitreous injection.~~

~~45. A sustained release biodegradable ocular implant comprising a hydrogel and at least about 150 µg of a tyrosine kinase inhibitor (TKI), wherein TKI particles are dispersed within the hydrogel, or a sustained release biodegradable ocular implant according to any of claims 1 to 29, for use in a method according to any of claims 30 to 44.~~

~~46. Use of a sustained release biodegradable ocular implant comprising a hydrogel and at least about 150 µg of a tyrosine kinase inhibitor (TKI), wherein TKI particles are dispersed within the hydrogel, or a sustained release biodegradable ocular implant according to any of claims 1 to 29, for the preparation of a medicament for use in a method according to any of claims 30 to 44.~~

~~47. A method of manufacturing the sustained release biodegradable ocular implant according to any of claims 1 to 29, the method comprising the steps of forming a hydrogel comprising a polymer network and TKI particles dispersed within the hydrogel, shaping the hydrogel and drying the hydrogel.~~

~~48. The method of claim 47, wherein the polymer network is formed by mixing and reacting an electrophilic group-containing multi-arm PEG precursor with a nucleophilic group-containing multi-arm PEG precursor or another nucleophilic group-containing crosslinking agent in a buffered solution in the presence of TKI particles and allowing the mixture to gel to form the hydrogel.~~

27. A method of manufacturing the sustained release biodegradable ocular implant of any of claims 1 to 20, the method comprising the steps of forming a hydrogel by mixing and reacting an electrophilic group-containing multi-arm PEG precursor with a nucleophilic group-containing multi-arm PEG precursor or another nucleophilic group-containing crosslinking agent in a buffered solution in the presence of axitinib particles, allowing the mixture to gel to form the hydrogel, and drying the hydrogel.

~~49~~28. The method of claim ~~47 or 48~~27, comprising ~~shaping the hydrogel by means of~~ casting the mixture into a tubing ~~to form a hydrogel strand~~ prior to complete gelling of the hydrogel to form a hydrogel strand~~,~~.

~~50. The~~ the method ~~of claim 49,~~ further comprising stretching the hydrogel strand in the longitudinal direction prior to or after drying the hydrogel (wet stretching or dry stretching), preferably at a stretch factor of ~~about~~ 1 to ~~about~~ 4.5.

~~51. The method of claim 50, wherein the stretch factor is about 1.3 to about 3.5, preferably about 2 to about 2.5.~~

~~52~~29. A kit comprising one or more sustained release biodegradable ocular implant(s) of any of claims 1 to ~~29~~ 20 and one or more needles for injection~~, wherein each implant is loaded in a needle~~.

~~53~~30. The kit of claim ~~52~~29, wherein each implant is loaded in ~~the~~ a needle~~(s)~~ that ~~have~~ has a gauge size of 22 to 30.

~~54~~31. The kit of claim ~~52~~ 29 or ~~53~~30, wherein the lumen of each needle is occluded by a material that is solid at room temperature and soft or liquid at body temperature.

~~55~~32. The kit of any of claims ~~52~~ 29 to ~~54~~31, further comprising an injection device, wherein each needle is ~~pre-connected~~ or is not pre-connected to the injection device.