OBJECTS AND SUMMARY OF THE 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 examples of the present 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 of the present 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 of the present 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 of the present 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 of the present 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 of the present disclosure 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 of the present disclosure 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 of the present disclosure 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 of the present disclosure 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 of the present disclosure 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 of the present disclosure 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 of the present disclosure 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 of the present disclosure 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 of the present disclosure 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 of the present disclosure 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 of the present disclosure 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 of the present disclosure 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 of the present disclosure 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 of the present disclosure 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 of the present disclosure is to provide an ocular implant comprising a TKI such as axitinib that is safe and well tolerated.

[00035] Another object of certain examples of the present disclosure 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 of the present disclosure 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 of the present disclosure 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 of the present disclosure 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 of the present disclosure 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 of the present disclosure 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 of the present disclosure 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 of the present disclosure 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 of the present disclosure 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 of the present disclosure 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 of the present disclosure 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 of the present disclosure 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 of the present disclosure 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 of the present disclosure 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 of the present disclosure is to provide a method of manufacturing an ocular implant comprising a TKI such as axitinib.

[00050] Another object of certain examples of the present disclosure 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 of the present disclosure is to provide a method of minimizing potential tissue damage during injection of an ocular implant.

[00052] Another object of certain examples of the present disclosure 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 of the present disclosure 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 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 of the present disclosure 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 of the present disclosure 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 the present disclosure 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 and others are solved by one or more examples as disclosed and claimed herein.

[00059] The individual examples of the present disclosure are disclosed in the specification and claimed in the independent claims, while the dependent claims claim particular examples and variations of these examples of the disclosure. Details of the various examples of the present disclosure 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 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.

2. The sustained release biodegradable ocular implant of claim 1, wherein the implant comprises axitinib in an amount of 480 µg to 750 µg or 320 µg to 500 µg or 160 µg to 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.

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 0.2 mg to 1.5 mg, preferably a total weight of 0.75 mg to 1.25 mg.

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 10 mm and a diameter of equal to or less than 0.8 mm.

6. 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 5, preferably less than 2.25, and/or has a ratio of the length in the dry state to the length in the hydrated state of greater than 0.7, preferably greater than 0.8.

7. The sustained release biodegradable ocular implant of any of the preceding claims, wherein the implant provides for the release of axitinib at an average rate of 0.25 µg to 2.5 µg per day, preferably of 0.25 µg to 1.5 µg per day, more preferably of 0.3 µg to 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.

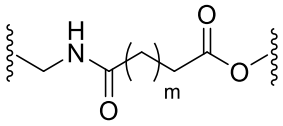
8. The sustained release biodegradable ocular implant of any of the preceding claims, wherein the implant is an intravitreal implant.

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

11. The sustained release biodegradable ocular implant of 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 10,000 to 60,000 Daltons, preferably 20,000 Daltons.

12. The sustained release biodegradable ocular implant of claim 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.

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

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

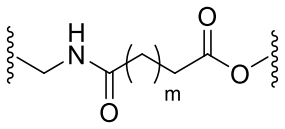
15. The sustained release biodegradable ocular implant of any of the preceding claims, wherein the axitinib particles have a d90 particle size of less than 30 µm as determined by laser diffraction.

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).

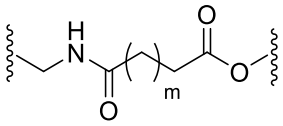
19. The sustained release biodegradable ocular implant of claim 1, wherein the implant is an intravitreal implant and comprises from 480 µg to 750 µg axitinib, is cylindrical and has in its dry state a length of less than or equal to 10 mm and a diameter of 0.3 mm to 0.4 mm, and in its hydrated state (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.

22. The sustained release biodegradable ocular implant of claim 21 for use in treating AMD during a treatment period of at least 3 months, or at least 6 months, or at least 9 months, or at least 12 months.

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

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

25. The sustained release biodegradable ocular implant for use in treating AMD of any of claims 21 to 24, wherein concurrently or in combination with the treatment with the 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.

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.

28. The method of claim 27, comprising casting the mixture into a tubing prior to complete gelling of the hydrogel to form a hydrogel strand,the method 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 1 to 4.5.

29. A kit comprising one or more sustained release biodegradable ocular implant(s) of any of claims 1 to 20 and one or more needles for injection.

30. The kit of claim 29, wherein each implant is loaded in a needle that has a gauge size of 22 to 30.

31. The kit of claim 29 or 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.

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