OCULAR IMPLANT CONTAINING AN ACTIVE AGENT

TECHNICAL FIELD

[0001] The present invention relates to the treatment of ocular diseases. According to the present invention, ocular diseases are treated by administering an implant that is biodegradable and provides sustained release of an active agent suitable for ocular therapy.

BACKGROUND

[0002] There are many ocular diseases that can be treated with pharmacotheraopy. The problem with pharmacotherapy is that systemic administration is not ideal because high levels of systemic dosing is required to achieve effective intraocular concentrations. This leads to the increased incidence of unacceptable side effects. Similarly, ocular instillation of active agents (e.g. eye drops) is often ineffective because therapeutic levels of drug in the middle or back portions of the eye are often not achieved and drug concentration is difficult to control due to wash out, user error, and other factors. Other local therapy routes such as intravitreal injection have failed because such delivery routes tend to result in short half-life and rapid clearance, without sustained release capability being attained. Additionally, daily injections are frequently required to maintain therapeutic ocular drug levels, which is not tolerable to many patients. Some active agents are poorly soluble and are injected as a suspension. These solid particulates, however, can settle onto the retina or migrate to contact the lens or even move into the anterior chamber and lead to localized toxic effects.

[0003] The use of ocular implants for drug delivery offers many advantages over traditional drops or injections. These devices are typically placed in or adjacent to the eye tissues and offer better drug release and treatment duration potential. Although ocular implant devices have improved over the years, there are still many deficiencies. First, not all ocular implants are biodegradable, leaving a permanent foreign object or requiring tedious removal procedures following drug administration. Additionally, most biodegradable implants do not completely dissolve until long after their useful lifespan. The user is therefore left with implant residues that may accumulate with repeat treatment and/or interfere with vision. Next, some ocular implants consist of complicated multiple layers requiring extensive manufacturing processes. This leads to increased production costs and time, and raises the likelihood of contamination from additional handling. Also, formulations containing hydrophobic drugs with biodegradable matrices can result in very little or no release of active agent until erosion of the network occurs. This can lead to drug-dumping, which provides little benefit and causes toxicity issues. Finally, in instances where the drug has low solubility the use of ocular implants have proven less successful because of the delicate balance between long term sustained release and the risk of unwanted particle suspension and migration in the middle or back of the eye.

[0004] There continues to exist a need in the art for ocular implants to treat ocular disease.

[0005] All references disclosed herein are hereby incorporated by reference in their entireties for all purposes.

OBJECTS AND SUMMARY OF THE INVENTION

[0005a] In an aspect of the present disclosure, there is provided a sustained release biodegradable ocular implant comprising a hydrogel and an active agent, wherein the active agent is not a tyrosine kinase inhibitor, wherein the hydrogel comprises a polymer network comprising polyethylene glycol (PEG) units, wherein active agent particles are dispersed within the hydrogel, and wherein the implant is cylindrical and in its dry state has a length of less than 17 mm.

[0005b] In another aspect, there is provided a sustained release biodegradable ocular implant as defined above for the treatment of age-related macular degeneration.

[0005c] In another aspect, there is provided a use of a sustained release biodegradable ocular implant as defined above in the preparation of a medicament for the treatment of neovascular age-related macular degeneration.

[0006] It is an object of certain ~~embodiments~~ examples of the present ~~invention~~ disclosure to provide an ocular implant comprising an active agent 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.

[0007] Another object of certain ~~embodiments~~ examples of the present ~~invention~~ disclosure is to provide an ocular implant comprising an active agent that provides for sustained release of the active agent into the eye.

[0008] Another object of certain ~~embodiments~~ examples of the present ~~invention~~ disclosure is to provide an ocular implant comprising an active agent that is pre-loaded into a syringe, thereby avoiding contamination of the implant prior to injection as no further preparation steps are needed.

[0009] Another object of certain ~~embodiments~~ examples of the present ~~invention~~ disclosure is to provide an ocular implant comprising an active agent that is sufficiently biodegradable, i.e., cleared from the eye within a time coinciding with the active agent 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.

[00010] Another object of certain ~~embodiments~~ examples of the present ~~invention~~ disclosure is to provide an ocular implant comprising an active agent that is biodegradable, wherein decomposition of the implant into smaller particles that may e.g. impact vision are avoided during implant degradation.

[00011] Another object of certain ~~embodiments~~ examples of the present ~~invention~~ disclosure is to provide an ocular implant comprising an active agent, 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.

[00012] Another object of certain ~~embodiments~~ examples of the present ~~invention~~ disclosure is to provide an ocular implant comprising an active agent that is biocompatible and non-immunogenic due to the implant being free or substantially free of animal- or human-derived components.

[00013] Another object of certain ~~embodiments~~ examples of the present disclosure~~invention~~ is to provide an ocular implant comprising an active agent that is free of preservatives, such as antimicrobial preservatives.

[00014] Another object of certain examples~~embodiments~~ of the present disclosure~~invention~~ is to provide an ocular implant comprising an active agent that is easy to inject, in particular intravitreally.

[00015] Another object of certain examples~~embodiments~~ of the present disclosure~~invention~~ is to provide an ocular implant comprising an active agent that contains a therapeutically effective amount of the active agent but is relatively small in length and/or diameter.

[00016] Another object of certain examples~~embodiments~~ of the present disclosure~~invention~~ is to provide an ocular implant comprising an active agent that is dimensionally stable when in a dry state but changes its dimensions upon hydration, e.g. after administration to the eye.

[00017] Another object of certain examples~~embodiments~~ of the present disclosure~~invention~~ is to provide an ocular implant comprising an active agent 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.

[00018] Another object of certain examples~~embodiments~~ of the present disclosure~~invention~~ is to provide an ocular implant comprising an active agent that is injected in a dry form and hydrates *in situ* (i.e. in the eye) when injected.

[00019] Another object of certain examples~~embodiments~~ of the present disclosure ~~invention~~ is to provide an ocular implant comprising an active agent that when placed in the eye has low cative agent concentration at the implant surface thereby avoiding toxicity of the active agent when the implant gets in contact with ocular cells or tissues such as the retina.

[00020] Another object of certain examples~~embodiments~~ of the present disclosure~~invention~~ is to provide an ocular implant comprising an active agent 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).

[00021] Another object of certain examples~~embodiments~~ of the present disclosure ~~invention~~ is to provide an ocular implant comprising an active agent that is easy to handle, in particular that does not spill or fragment easily.

[00022] Another object of certain examples~~embodiments~~ of the present disclosure~~invention~~ is to provide an ocular implant comprising an active agent that enables administration of an exact dose (within a broad dose range), thereby avoiding the risk of over- and under-dosing.

[00023] Another object of certain examples~~embodiments~~ of the present disclosure~~invention~~ is to provide an ocular implant comprising an active agent that generally stays in the area of the eye to which it was administered.

[00024] Another object of certain examples~~embodiments~~ of the present disclosure ~~invention~~ is to provide an ocular implant comprising an active agent wherein the implant causes minimal or no visual impairment after administration.

[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 safe and well tolerated.

[00026] Another object of certain examples~~embodiments~~ of the present disclosure~~invention~~ is to provide an ocular implant comprising an active agent that does not induce severe adverse events, such as severe ocular adverse events.

[00027] Another object of certain examples~~embodiments~~ of the present disclosure~~invention~~ is to provide an ocular implant comprising an active agent that provides for sustained release of a therapeutically effective amount of the active agent 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.

[00028] Another object of certain examples~~embodiments~~ of the present disclosure~~invention~~ is to provide an ocular implant comprising an active agent that provides for sustained release of the active agent 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.

[00029] Another object of certain examples~~embodiments~~ of the present disclosure~~invention~~ is to provide an ocular implant comprising an active agent that provides for sustained release the active agent 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.

[00030] Another object of certain examples~~embodiments~~ of the present disclosure~~invention~~ is to provide an ocular implant comprising an active agent 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 catiev agent 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.

[00031] Another object of certain examples~~embodiments~~ of the present disclosure~~invention~~ is to provide an ocular implant comprising an active agent that provides for sustained release of the active agent 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 active agent are observed in ocular tissues such as the retina and the choroid, as well as the vitreous humor over this period of time.

[00032] Another object of certain examples~~embodiments~~ of the present disclosure~~invention~~ is to provide an ocular implant comprising an active agent that provides for sustained release of the active agent 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 active agent is not accumulating in the anterior chamber of the eye.

[00033] Another object of certain examples~~embodiments~~ of the present disclosure~~invention~~ is to provide an ocular implant comprising ab active agent that provides sustained release of an active agent 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 active is not or is not substantially resorbed systemically thereby substantially avoiding systemic toxicity.

[00034] 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.

[00035] 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.

[00036] 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.

[00037] 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.

[00038] 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.

[00039] 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.

[00040] Another object of certain examples~~embodiments~~ of the present disclosure ~~invention~~ is to provide a method of manufacturing an ocular implant comprising an active agent.

[00041] 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.

[00042] 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.

[00043] Another object of certain examples~~embodiments~~ of the present disclosure~~invention~~ is to provide a kit comprising one or more ocular implants comprising an active agent and optionally comprising a means for injecting the ocular implant.

[00044] 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.

[00045] 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.

[00046] 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.

[00047] 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.

[00048] 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).

[00049] 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.

[00050] The individual ~~aspects~~ examples 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.

[00051] 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

[00052] **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.

[00053] **Figure 2** Schematic representation of one embodiment of implant localization. After injection the implant hydrates in situ while maintaining a cylindrical shape. The implant is localized in the posterior part of the eye.

[00054] **Figure 3** Schematic representation of hydrogel biodegradation over time. As the drug is released, a clearance zone is formed (black) as low solubility drug particles (white) gradually dissolve and drug diffuses from hydrogel to the aqueous surrounding (as for instance the vitreous humor). Over time, the gel degrades and is resorbed, while drug diffuses out. During the degradation process, the gel gradually swells until degradation is advanced to the point of shrinkage and distortion.

CLAIMS

1. A sustained release biodegradable ocular implant comprising a hydrogel and an active agent, wherein the active agent is not a tyrosine kinase inhibitor, wherein the hydrogel comprises a polymer network comprising polyethylene glycol (PEG) units, wherein active agent particles are dispersed within the hydrogel, and wherein the implant is cylindrical and in its dry state has a length of less than ~~about~~ 17 mm~~, wherein the active agent is not a tyrosine kinsase inhibitor~~.

2. The sustained release biodegradable ocular implant according to claim 1, 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.

3. The sustained release biodegradable ocular implant of claim 1 or 2, wherein the active agent is an active agent suitable for the treatment of age-related macular degeneration.

4. The sustained release biodegradable ocular implant of any of the preceding claims, wherein the active agent is avacincaptad pegol.

5. 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.

6. 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.

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

8. The sustained release biodegradable ocular implant of any of the preceding claims, wherein the implant provides for the release of the active agent 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.

9. The sustained release biodegradable ocular implant of any of the preceding claims, wherein the polymer network is formed by 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.

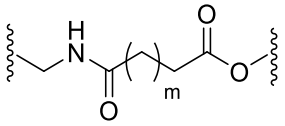
10. The sustained release biodegradable ocular implant of claim 9, wherein the electrophilic group is a N-hydroxysuccinimidyl (NHS) ester end group, preferably a succinimidylazelate (SAZ) end group, a succinimidyladipate (SAP) end group, a succinimidylglutarate (SG) end group, and/or a succinimidylsuccinate (SS) end group or a combination of any of these, and the nucleophilic group is an amine group.

11. The sustained release biodegradable ocular implant of any of the preceding claims, wherein the hydrogel comprises multi-arm PEG units, preferably 4-arm and/or 8-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.

12. The sustained release biodegradable ocular implant of any of the preceding claims, wherein the PEG units are 4a20k and/or 8a20k PEG units.

13. The sustained release biodegradable ocular implant of any of claims 9 to 12, wherein the polymer network is formed by reacting the electrophilic group-containing PEG precursor 4a20kPEG-SAZ with the nucleophilic group-containing PEG precursor 8a20kPEG-NH_2.

14. The sustained release biodegradable ocular implant of any of the preceding claims, 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 m is 6.

15. A sustained release biodegradable ocular implant according to any of the preceding claims for the treatment of age-related macular degeneration.

~~2. The sustained release biodegradable ocular implant of claim 1, wherein the active agent is selected from immunosuppressants, complement protein C5 agents, steroids, anti-inflammatories, antivirals, antibiotics, anti-glaucoma agents, anti-VEGF agents, analgesics and combinations thereof.~~

~~3. The sustained release biodegradable ocular implant of claim 1 or 2, wherein the active agent is an immunosuppressant.~~

~~4. The sustained release biodegradable ocular implant of claim 3, wherein the immunosuppressant is selected from cyclosporine, mTOR inhibitors (e.g., rapamycin, tacrilimus, temsirolimus, sirolimus, everolimus, KU-0063794, WYE-354, AZD8055, metformin, or Torin-2), cyclophosphamide, atoposide, thiotepa, methotrexate, azathioprine, mercaptopurine, interferons, infliximab, etanercept, mycophenolate mofetil, 15-deoxyspergualin, thalidomide, glatiramer, leflunomide, vincristine, cytarabine, pharmaceutically acceptable salts thereof or combinations thereof.~~

~~5. The sustained release biodegradable ocular implant of claim 1 or 2, wherein the active agent is a complement protein C5 agent.~~

~~6. The sustained release biodegradable ocular implant of claim 5, wherein the complement protein C5 agent is eculizumab or avacincaptad pegol.~~

~~7. The sustained release biodegradable ocular implant of claim 1 or 2, wherein the active agent is a steroid.~~

~~8. The sustained release biodegradable ocular implant of claim 7, wherein the steroid is selected from dexamethasone, budensonide, triamcinolone, hydrocortisone, loteprednol, prednisolone, mometasone, fluticasone, rimexolone, fluorometholone, beclomethasone, flunisolide, pharmaceutically acceptable salts thereof and combinations thereof.~~

~~9. The sustained release biodegradable ocular implant of claim 1 or 2, wherein the active agent is an anti-inflammatory.~~

~~10. The sustained release biodegradable ocular implant of claim 9, wherein the anti-inflammatory is a COX 1 inhibitor.~~

~~11. The sustained release biodegradable ocular implant of claim 9, wherein the anti-inflammatory is a COX 2 inhibitor.~~

~~12. The sustained release biodegradable ocular implant of claim 9, wherein the anti-inflammatory is selected from salicylates, propionic acid derivatives, acetic acid derivatives, enolic acid derivatives, and anthranilic acid derivatives.~~

~~13. The sustained release biodegradable ocular implant of claim 9, wherein the anti-inflammatory is selected from acetylsalicylic acid, diflunisal, salsalate, ibuprofen, dex-ibuprofen, naproxen, fenoprofen, ketoprofen, dex-ketoprofen, flurbiprofen, oxaprozin, loxoprofen, indomethacin, tolmetin, sulindac, etodolac, ketorolac, diclofenac, aceclofenac, nabumetone, piroxicam, tenoxicam, tenoxicam, loroxicam, phenylbutazone, mefenamic acid, meclofenamic acid, flufenamic acid, tolfenamic acid, celecoxib, pharmaceutically acceptable salts thereof and combinations thereof.~~

~~14. The sustained release biodegradable ocular implant of claim 1 or 2, wherein the active agent an analgesic and is selected from acetaminophen, acetaminosalol, aminochlorthenoxazin, acetylsalicylic 2-amino-4-picoline acid, acetylsalicylsalicylic acid, anileridine, benoxaprofen, benzylmorphine, 5-bromosalicylic acetate acid, bucetin, buprenorphine, butorphanol, capsaicin, cinchophen, ciramadol, clometacin, clonixin, codeine, desomorphine, dezocine, dihydrocodeine, dihydromorphine, dimepheptanol, dipyrocetyl, eptazocine, ethoxazene, ethylmorphine, eugenol, floctafenine, fosfosal,~~

glafenine, hydrocodone, hydromorphone, hydroxypethidine, ibufenac, p-lactophenetide, levorphanol, meptazinol, metazocine, metopon, morphine, nalbuphine, nicomorphine, norlevorphanol, normorphine, oxycodone, oxymorphone, pentazocine, phenazocine, phenocoll, phenoperidine, phenylbutazone, phenylsalicylate, phenylramidol, salicin, salicylamide, tiorphan, tramadol, diacerein, actarit, pharmaceutically acceptable salts thereof and combinations thereof.

15. The sustained release biodegradable ocular implant of claim 1 or 2, wherein the active agent is an antibiotic and is selected from penicillins, cephalosporins, fluoroquinolones, macrolides, and combinations thereof.

16. The sustained release biodegradable ocular implant of claim 1 or 2, wherein the active agent is an anti-viral and is selected from abacavir, aciclovir, acyclovir, adefovir, amantadine, amprenavir, ampligen, arbidol, atazanavir, boceprevir, cidofovir, darunavir, delavirdine, didanosine, docosanol, edoxudine, efavirenz, emtricitabine, enfuvirtide, entecavir, famciclovir, fomivirsen, fosamprenavir, foscarnet, fosfonet, ganciclovir, ibacitabine, imunovir, idoxuridine, imiquimod, indinavir, inosine, interferon type III, interferon type II, interferon type I, interferon, lamivudine, lopinavir, loviride, maraviroc, moroxydine, methisazone, nelfinavir, nevirapine, nexavir, oseltamivir, peginterferon alfa-2a, penciclovir, peramivir, pleconaril, podophyllotoxin, raltegravir, ribavirin, rimantadine, ritonavir, pyramiding saquinavir, stavudine, tenofovir, tenofovir disoproxil, tipranavir, trifluridine, trizivir, tromantadine, truvada, valaciclovir, valganciclovir, vicriviroc, vidarabine, viramidine, zalcitabine, zanamivir, zidovudine, pharmaceutically acceptable salts thereof and combinations thereof.

17. The sustained release biodegradable ocular implant of any preceding claim, wherein the administration is to a route selected from punctal, intravitreal, subconjunctival, intrascleral, subretinal, subachoroidal, periocular, peribulbar, retrobulbar, intracorneal, posterior sub-Tenon's delivery, anterior sub-Tenon's delivery, cul-de-sac delivery, or fornix delivery.

18. The sustained release biodegradable ocular implant of any of the preceding claims, wherein the tyrosine kinase inhibitor particles are dispersed within the hydrogel.

19. The sustained release biodegradable ocular implant of claim 18, wherein the tyrosine kinase inhibitor particles are micronized particles.

20. The sustained release biodegradable ocular implant of any of the preceding claims, wherein the implant is in a dried state prior to administration and becomes hydrated once administered into the eye.

21. 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 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.

22. The sustained release biodegradable ocular implant of claim 21, wherein the hydrogel comprises a polymer network that comprises crosslinked polymer units that are identical or different.

23. The sustained release biodegradable ocular implant of claim 22, wherein crosslinked polymer units are one or more crosslinked polyethylene glycol units.

24. The sustained release biodegradable ocular implant of any of claims 21 to 23, wherein the polymer network comprises polyethylene glycol units having an average molecular weight in the range from about 2,000 to about 100,000 Daltons.

25. The sustained release biodegradable ocular implant of claim 24, wherein the polyethylene glycol units have an average molecular weight in the range from about 10,000 to about 60,000 Daltons.

26. The sustained release biodegradable ocular implant of claim 25, wherein the polyethylene glycol units have an average molecular weight in the range from about 20,000 to about 40,000 Daltons.

27. The sustained release biodegradable ocular implant of claim 26, wherein the polyethylene glycol units have an average molecular weight of about 20,000 Daltons.

28. The sustained release biodegradable ocular implant of any of claims 21 to 27, wherein the polymer network comprises one or more crosslinked multi-arm polymer units.

29. The sustained release biodegradable ocular implant of claim 28, wherein the multi-arm polymer units comprise one or more 2- to 10-arm polyethylene glycol units.

30. The sustained release biodegradable ocular implant of claim 29, wherein the multi-arm polymer units comprise one or more 4- to 8-arm polyethylene glycol units.

31. The sustained release biodegradable ocular implant of claim 30, wherein the multi-arm polymer units comprise one or more 4-arm polyethylene glycol units.

32. The sustained release biodegradable ocular implant of any of claims 21 to 31, wherein the polymer network comprises both 4-arm and 8-arm polyethylene glycol units.

33. The sustained release biodegradable ocular implant of any of claims 21 to 32, wherein the polymer network is formed by reacting an electrophilic group-containing multi-arm polymer precursor with a nucleophilic group-containing multi-arm polymer precursor.

34. The sustained release biodegradable ocular implant of any of claims 21 to 33, wherein the electrophilic group is an amine group.

35. The sustained release biodegradable ocular implant of any of claims 21 to 34, wherein the nucleophilic group is an activated ester group.

36. The sustained release biodegradable ocular implant of claim 35, wherein the nucleophilic group is an N-hydroxysuccinimidyl (NHS) group.

37. The sustained release biodegradable ocular implant of claim 36, wherein the nucleophilic group is a succinimidylazelate (SAZ) group.

38. The sustained release biodegradable ocular implant of any of claims 32 to 37, wherein the 4-arm polyethylene glycol units are 4a20kPEG units and the 8-arm polyethylene glycol units are 8a20kPEG units.

39. The sustained release biodegradable ocular implant of claim 38, wherein the polymer network is obtained by reacting 4a20kPEG-SAZ with 8a20kPEG-NH_2 in a weight ratio of about 2:1 or less.

40. The sustained release biodegradable ocular implant of any of claims 1 to 39, wherein the implant in a dried state contains from about 25% to about 75% by weight of the tyrosine kinase inhibitor and from about 20% to about 60% by weight polymer units.

41. The sustained release biodegradable ocular implant of claim 40, wherein the implant in a dried state contains from about 35% to about 65% by weight of the tyrosine kinase inhibitor and from about 25% to about 50% by weight polymer units.

42. The sustained release biodegradable ocular implant of claim 41, wherein the implant in a dried state contains from about 45% to about 55% by weight of the tyrosine kinase inhibitor and from about 37% to about 47% by weight polymer units.

43. The sustained release biodegradable ocular implant of any of the preceding claims, wherein the implant contains one or more phosphate, borate or carbonate salt(s).

44. The sustained release biodegradable ocular implant of claim 43, wherein the implant contains phosphate salt originating from phosphate buffer used during the preparation of the hydrogel.

45. The sustained release biodegradable ocular implant of any of the preceding claims, wherein the hydrogel in a wet state contains about 3% to about 20% polyethylene glycol representing the polyethylene glycol weight divided by the fluid weight x 100.

46. The sustained release biodegradable ocular implant of claim 45, wherein the hydrogel contains about 7.5% to about 15% polyethylene glycol representing the polyethylene glycol weight divided by the fluid weight x 100.

47. The sustained release biodegradable ocular implant of any of the preceding claims, wherein the implant in a dried state contains not more than about 1 % by weight water.

48. The sustained release biodegradable ocular implant of any of the preceding claims, wherein the implant has an essentially cylindrical shape or another shape such as a cross shape.

49. The sustained release biodegradable ocular implant of any of the preceding claims, wherein the implant is in the form of a fiber.

50. The sustained release biodegradable ocular implant of any of the preceding claims, wherein the implant is administered to the eye through a needle.

51. The sustained release biodegradable ocular implant of claim 50, wherein the needle is a 25- or 27-gauge needle.

52. The sustained release biodegradable ocular implant of any of the preceding claims, wherein upon hydration in vivo in the eye or in vitro the diameter of the implant is increased, or the length of the implant is decreased while its diameter is increased.

53. The sustained release biodegradable ocular implant of claim 52, wherein hydration is measured in vitro in phosphate-buffered saline at a pH of 7.2 at 37 °C after 24 hours.

54. The sustained release biodegradable ocular implant of any of claims 17 to 53, wherein the implant biodegrades in the vitreous humor within about 2 to about 15 months after administration.

55. The sustained release biodegradable ocular implant of claim 54, wherein the implant biodegrades in the vitreous humor within about 4 to about 13 months after administration.

56. The sustained release biodegradable ocular implant of claim 55, wherein the implant biodegrades in the vitreous humor within about 9 to about 12 months after administration.

57. The sustained release biodegradable ocular implant of any of claims 2 to 56, wherein the implant after administration to the eye releases a therapeutically effective amount of active agent over a period of at least about 3 months, at least about 6 months, at least about 9 months, at least about 10 months, at least about 11 months, or at least about 12 months after administration.

58. The sustained release biodegradable ocular implant of claim 57, wherein the implant after administration to the eye releases a therapeutically effective amount of active agent over a period of at least 6 months.

59. The sustained release biodegradable ocular implant of claim 57, wherein the implant after administration to the eye releases a therapeutically effective amount of active agent over a period of at least 9 months.

60. The sustained release biodegradable ocular implant of any of claims 17 to 59, wherein active agent is released from the implant after administartion at an average rate of about 0.1 µg/day to about 10 µg/day.

61. The sustained release biodegradable ocular implant of claim 60, wherein active is released from the implant at an average rate of about 0.5 µg/day to about 7 µg/day.

62. The sustained release biodegradable ocular implant of claim 61, wherein active agent is released from the implant at an average rate about 1 µg/day to about 5 µg/day.

63. The sustained release biodegradable ocular implant of any of claims 17 to 62, wherein the implant biodegrades in the eye prior to complete solubilization of the active agent particles contained in the implant.

64. The sustained release biodegradable ocular implant of any of claims 17 to 63, wherein the entire amount of the active agent contained in the implant is released prior to the complete degradation of the implant in the eye.

65. The sustained release biodegradable ocular implant of any of the preceding claims, wherein the implant is obtainable by preparing a mixture containing hydrogel precursors and an active agent, filling the mixture into a tubing, allowing the hydrogel to gel in the tubing to provide a hydrogel shaped as a fiber, and stretching the hydrogel fiber.

66. The sustained release biodegradable ocular implant of claim 65, wherein the fiber has been stretched and/or twisted prior to or after drying.

67. The sustained release biodegradable ocular implant of claim 66, wherein the fiber has been stretched by a stretch factor in the longitudinal direction of from about 1.0 to about 4.5.

68. A sustained release biodegradable ocular implant containing an active agent dispersed in a hydrogel, wherein the hydrogel comprises a polymer network comprising polyethylene glycol units, and wherein the implant is in a dried state prior to administration.

69. The sustained release biodegradable ocular implant of claim 68, wherein the polymer network is formed by reacting 4a20kPEG-SAZ with 8a20kPEG-NH_2.

70. The sustained release biodegradable ocular implant of claim 69, wherein the hydrogel when formed and before being dried contains 7.5% polyethylene glycol, representing the polyethylene glycol weight divided by the fluid weight x 100.

71. The sustained release biodegradable ocular implant of any of claims 68 to 70, wherein the implant in a dried state contains from about 45% to about 55% by weight active agent and from about 37% to about 47% by weight polyethylene glycol units.

72. The sustained release biodegradable ocular implant of any of claims 68 to 71, wherein the implant in a dried state contains not more than about 1 % by weight water.

73. The sustained release biodegradable ocular implant of any of claims 68 to 72, wherein the polymer network is formed by reacting 4a20kPEG-SAZ with 8a20kPEG-NH_2 in a weight ratio of about 2:1 or less.

74. The sustained release biodegradable ocular implant of any of claims 68 to 73, wherein the implant releases in vitro about 0.01 µg to about 0.15 µg of active agent per day in phosphate-buffered saline at 37 °C for a period of 30 days.

75. The sustained release biodegradable ocular implant of any of claims 68 to 74, wherein the implant releases in vitro about 35 % to about 45 % of the active agent in 3 days, about 65 % to about 75 % of the active agemt in 7 days, and about 90 % to about 100 % of the active agent in 12 to 13 days in a 25:75 ethanol/water mixture (v/v) at 37 °C.

76. The sustained release biodegradable ocular implant of any of claims 68 to 75, wherein the implant releases in vitro about 25 % to about 35 % of the active agent in 2 months, about 47 % to about 57 % of the active agent in 3 months, about 70 % to about 80 % of the active agent in 5 months, and about 90 % to about 100 % of the active agent in 7 months in phosphate buffered saline at a pH of 7.2, at 37 ºC and with an octanol top layer.

77. The sustained release biodegradable ocular implant of any of claims 68 to 76, wherein the implant is in the form of a fiber that has an average length of about 15 mm to about 16.5 mm and an average diameter of about 0.20 mm to about 0.30 mm in its dried state.

78. The sustained release biodegradable ocular implant of claim 77, which decreases in length and increases in diameter upon hydration in vivo in the eye or in vitro, wherein hydration in vitro is measured in phosphate-buffered saline at a pH of 7.2 at 37 °C after 24 hours.

79. The sustained release biodegradable ocular implant of claim 77 or 78, wherein the implant in its hydrated state has an average length of about 6.5 to about 8 mm and an average diameter of about 0.70 to about 0.80 mm.

80. The sustained release biodegradable ocular implant of any of claims 68 to 79, wherein the implant is obtainable by preparing a mixture containing hydrogel precursors and active agent, filling the mixture into a tubing, allowing the hydrogel to gel in the tubing to provide a hydrogel shaped as a fiber, and stretching the hydrogel fiber.

81. The sustained release biodegradable ocular implant of claim 80, wherein the fiber is stretched after drying by a factor of about 2 to about 5.

82. The sustained release biodegradable ocular implant of claim 81, wherein the fiber is stretched after drying by a factor of about 3 to about 4.5.

83. The sustained release biodegradable ocular implant of any of claims 68 to 82, wherein the implant in a dried state is loaded in a needle, such as a 25-gauge needle or a 27-gauge needle, for injection into the eye.

84. A sustained release biodegradable ocular implant containing an active agent selected from immunosuppressants, complement protein C5 agents, steroids, anti-inflammatories, antivirals, antibiotics, anti-glaucoma agents, anti-VEGF agents, and analgesics dispersed in a hydrogel, wherein the hydrogel comprises a polymer network.

85. The sustained release biodegradable ocular implant of claim 84, wherein the polymer network comprises crosslinked polyethylene glycol units.

86. The sustained release biodegradable ocular implant of claim 85, wherein the active agent is an immunosuppressant.

87. The sustained release biodegradable ocular implant of claim 86, wherein the active agent is an antibiotic.

88. The sustained release biodegradable ocular implant of any of claims 84 to 87, wherein the polyethylene glycol units comprise 4-arm and/or 8-arm polyethylene glycol units having an average molecular weight in the range from about 10,000 Daltons to about 60,000 Daltons.

89. The sustained release biodegradable ocular implant of claim 88, wherein the polyethylene glycol units comprise 4a20kPEG units.

90. The sustained release biodegradable ocular implant of claim 89, wherein the polymer network is formed by reacting 4a20kPEG-SAZ with 8a20kPEG-NH_2.

91. The sustained release biodegradable ocular implant of claim 90, wherein the weight ratio of 4a20kPEG-SAZ to 8a20kPEG-NH_2 is about 2:1 or less.

92. The sustained release biodegradable ocular implant of any of claims 84 to 91, wherein the implant in a dried state contains from about 45% to about 55% by weight active agent and from about 37% to about 47% by weight polyethylene glycol units.

93. The sustained release biodegradable ocular implant of any of claims 84 to 92, wherein the implant in a dried state contains not more than about 1% by weight water.

94. The sustained release biodegradable ocular implant of any of claims 84 to 93, wherein the implant is in the form of a fiber that in its dried state has an average length of about 7 mm to about 12 mm and an average diameter of about 0.25 mm to about 0.50 mm.

95. The sustained release biodegradable ocular implant of claim 94, wherein the implant is in the form of a fiber that in its dried state has an average length of about 8 mm to about 11 mm and an average diameter of about 0.3 mm to about 0.4 mm.

96. The sustained release biodegradable ocular implant of any of claims 84 to 95, wherein the implant is for administration to a route selected from punctal, intravitreal, subconjunctival, intrascleral, subretinal, subachoroidal, periocular, peribulbar, retrobulbar, intracorneal, posterior sub-Tenon's delivery, anterior sub-Tenon's delivery, cul-de-sac delivery, or fornix delivery.

97. The sustained release biodegradable ocular implant of claim 94 to 96, which increases in diameter upon hydration in vivo in the eye or in vitro, wherein hydration in vitro is measured in phosphate-buffered saline at a pH of 7.2 at 37 °C after 24 hours.

98. The sustained release biodegradable ocular implant of claim 97, wherein the implant in its hydrated state has an average length of about 9 mm to about 12 mm and an average diameter of about 0.5 mm to about 0.8 mm,

99. The sustained release biodegradable ocular implant of claim 98, wherein the implant in its hydrated state has an average length of about 9.5 mm to about 11.5 mm and an average diameter of about 0.65 mm to about 0.75 mm or has an average length in its hydrated state of not more than about 10 mm or not more than about 9 mm.

~~100.The sustained release biodegradable ocular implant of any of claims 84 to 99, wherein the implant releases in vitro about 0.3 µg to about 0.5 µg of active agent per day in phosphate-buffered saline at 37 ºC for a period of 30 days.~~

~~101.The sustained release biodegradable ocular implant of any one of claims 84 to 100, wherein the implant releases in vitro about 40 % to about 60 % of the active agent in 2 days, about 65 % to about 85 % of the axitinib in 4 days, and about 75 % to about 90 % of the active agent in 6 days in a 25:75 ethanol/water mixture (v/v) at 37 ºC.~~

~~102.The sustained release biodegradable ocular implant of claim 101, wherein the implant releases in vitro about 45 % to about 55 % of the active agent in 2 days, about 70 % to about 80 % of the active agent in 4 days, and about 80 % to about 90 % of the active agent in 6 days in a 25:75 ethanol/water mixture (v/v) at 37 ºC.~~

~~103.The sustained release biodegradable ocular implant of any of claims 84 to 102, wherein the implant is obtainable by preparing a mixture containing hydrogel precursors and active agent, filling the mixture into a tubing, allowing the hydrogel to gel in the tubing to provide a hydrogel shaped as a fiber, and stretching the hydrogel fiber.~~

~~104.The sustained release biodegradable ocular implant of claim 103, wherein the fiber is wet-stretched prior to drying by a factor of about 0.5 to about 5.~~

~~105.The sustained release biodegradable ocular implant of claim 104, wherein the fiber is wet-stretched prior to drying by a factor of about 1 to about 4.~~

~~106.The sustained release biodegradable ocular implant of claim 105, wherein the fiber is wet-stretched prior to drying by a factor of about 1.5 to about 3.5.~~

~~107.The sustained release biodegradable ocular implant of claim 106, wherein the fiber is wet-stretched prior to drying by a factor of about 1.7 to about 3.~~

~~108.The sustained release biodegradable ocular implant of any of claims 84 to 107, wherein the implant in a dried state is loaded in a needle for injection into the vitreous humor.~~

~~109.The sustained release biodegradable ocular implant of claim 108, wherein the implant in a dried state is loaded in a 25-gauge or a 27-gauge needle.~~

~~110.The sustained release biodegradable ocular implant of any of claims 1 to 109, wherein the hydrogel comprises a polymer network which is semi-crystalline in the dry state at or below room temperature, and amorphous in the wet state.~~

~~111.The sustained release biodegradable ocular implant of any of claims 1 to 110, wherein the implant has undergone wet or dry stretching during manufacture, and wherein the implant in the stretched form is dimensionally stable when in the dry state at or below room temperature.~~

~~112.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 an active agent according to any of the preceding claims,.~~

~~113.The method of claim 112, wherein the active agent is an immunosupressant.~~

~~114.The method of claim 112, wherein the active agent is a complement protein C5 agent.~~

~~115.The method of claim 112, wherein the active agent is a steroid.~~

~~116.The method of claim 112, wherein the active agent is an anti-viral.~~

~~117.The method of claim 112, wherein the active agent is an anti-biotic.~~

~~118.The method of claim 112, wherein the active agent is an anti-glaucoma agent.~~

~~119.The method of claim 112, wherein the active agent is an anti-inflammatory.~~

120.The method of claim 119, wherein the anti-inflammatory is a COX-1 inhibitor.

121.The method of claim 119, wherein the anti-inflammatory is a COX-2 inhibitor.

122.The method of claim 112, wherein the delivery route is selected from punctal, intravitreal, subconjunctival, intrascleral, subretinal, subchoroidal, periocular, peribulbar, retrobulbar, intracorneal, posterior sub-Tenon's delivery, anterior sub-Tenon's delivery, cul-de-sac delivery, or fornix delivery .

123.The method of any of claims 112 to 122, wherein the ocular disease is in the back of the eyes.

124.The method of any of claims 112 to 122, wherein the ocular disease is in the front of the eye

125. The method of any of claims 112 to 122, wherein the ocular disease is a retinal disease including Choroidal Neovascularization, Diabetic Retinopathy, Diabetic Macular Edema, Retinal Vein Occlusion, Acute Macular Neuroretinopathy, Central Serous Chorioretinopathy, and Cystoid Macular Edema; wherein the ocular disease is Acute Multifocal Placoid Pigment Epitheliopathy, Behcet's Disease, Birdshot Retinochoroidopathy, Infectious (Syphilis, Lyme, Tuberculosis, Toxoplasmosis), Intermediate Uveitis (Pars Planitis), Multifocal Choroiditis, Multiple Evanescent White Dot Syndrome (MEWDS), Ocular Sarcoidosis, Posterior Scleritis, Serpignous Choroiditis, Subretinal Fibrosis, Uveitis Syndrome, or Vogt-Koyanagi-Harada Syndrome; wherein the ocular disease is a vascular disease or exudative diseases, including Coat's Disease, Parafoveal Telangiectasis, Papillophlebitis, Frosted Branch Angitis, Sickle Cell Retinopathy and other Hemoglobinopathies, Angioid Streaks, and Familial Exudative Vitreoretinopathy; or wherein the ocular disease results from trauma or surgery, including Sympathetic Ophthalmia, Uveitic Retinal Disease, Retinal Detachment, Trauma, Photodynamic Laser Treatment, Photocoagulation, Hypoperfusion During Surgery, Radiation Retinopathy, Bone Marrow Transplant, Retinopathy Rhodopsin-mediated autosomal dominant retinitis pigmentosa, Best1 related retinal diseases, Leber congentital amaurosis, Stargardt macular dystrophy or Inherited retinal disease.

126.The method of any of claims 112 to 124, wherein the ocular disease is neovascular age-related macular degeneration, diabetic macular edema or retinal vein occlusion.

127.The method of claim 126, wherein the disease is neovascular age-related macular degeneration.

128.The method of any of claims 112 to 127, wherein the treatment is effective in reducing the central subfield thickness as measured by optical coherence tomography in a patient whose central subfield thickness is elevated.

129.The method of any of claims 112 to 128, wherein the dose per eye administered once for the treatment period is contained in one implant or in two or more implants administered concurrently.

130.The method of any of claims 112 to 129, wherein the implant is administered by injection into the vitreous humor.

131.The method of any of claims 112 to 130, wherein the treatment period is at least 4.5 months, at least 6 months, at least 9 months, at least 11 months or at least 12 months.

132.The method of claim 131, wherein the treatment period is at least 6 months, at least 9 months, or at least 11 months.

133.The method of any of claims 112 to 132, wherein concurrently with the treatment with the sustained release ocular implant an anti-VEGF agent is administered to the patient.

134.The method of claim 133, wherein the anti-VEGF agent is selected from the group consisting ofbevacizumab, pegaptanib, ranibizumab, and brolucizumab.

135.The method of claim 134, wherein the anti-VEGF agent is bevacizumab.

136.The method of any of claims 133 to 135, wherein the anti-VEGF agent is administered by means of intravitreal injection.

137.The method of any of claims 112 to 136, wherein the patient receiving the implant has a history of an anti-VEGF treatment.

138.The method of any of claims 112 to 136, wherein the patient receiving the implant has no history of an anti-VEGF treatment (anti-VEGF naïve).

139.A method of treating neovascular age-related macular degeneration in a patient in need thereof, the method comprising administering to the patient a sustained release biodegradable ocular implant comprising a hydrogel that comprises a polymer network and a suitable active agent, wherein one implant per eye is administered once for a treatment period of at least 9 months, and wherein the patient has a history of an anti-VEGF treatment.

140.A method of treating neovascular age-related macular degeneration in a patient in need thereof, the method comprising administering to the patient a sustained release biodegradable ocular implant comprising a hydrogel that comprises a polymer network and a suitable active agent, wherein two implants per eye µg are administered once for a treatment period of at least 3 months, and wherein the patient has a history or has no history of an anti-VEGF treatment.

141.The method of claim 139 or 140, wherein the treatment results in a reduction in central subfield thickness (CSFT) as measured by optical coherence tomography during the treatment period.

142.The method of any of claims 139 to 141, wherein the active agent is dispersed in the hydrogel which comprises a polymer network formed by reacting 4a20kPEG-SAZ with 8a20kPEG-NH_2, and wherein the implant is in a dried state prior to administration.

143.The method of claim 142, wherein the hydrogel when formed and before being dried contains about 7.5% polyethylene glycol, representing the polyethylene glycol weight divided by the fluid weight x 100.

144.The method of any of claims 140 to 143 wherein the treatment period is at least 9 months.

145.A method of treating neovascular age-related macular degeneration in a patient in need thereof, the method comprising administering to the patient a sustained release biodegradable ocular implant comprising an active agent dispersed in a hydrogel comprising a polymer network, wherein the implant is administered once for a treatment period of at least 3 months.

146.The method of claim 145, wherein the active agent is an immunosuppressant.

147.The method of claim 146, wherein the active agent is an ant-viral.

148.The method of any of claims 145 to 147, wherein the implant is as defined in claims 84 to 111.

149.The method of any of claims 145 to 148, wherein the implant is administered into the vitreous humor.

150.The method of any of claims 145 to 149, wherein the treatment period is at least 6 months, at least 9 months, at least 11 months, or at least 12 months.

151.The method any of claims 145 to 150, wherein the implant is administered by injection into the vitreous humor by means of a 25- or a 27-gauge needle.

152.The method of any of claims 145 to 151, wherein the patient receiving the implant has a history of an anti-VEGF treatment, or has no history of an anti-VEGF treatment (anti-VEGF naïve).

153.The method of any of claims 145 to 152, wherein an anti-VEGF agent is administered to the patient concurrently with the implant.

154.The method of claim 153, wherein the anti-VEGF agent is selected from the group consisting of bevacizumab, pegaptanib, ranibizumab, and brolucizumab.

155.The method of claim 154, wherein the anti-VEGF agent is bevacizumab.

156.The method of any of claims 153 to 155, wherein the anti-VEGF agent is administered by means of intravitreal injection.

157.The method of any of claims 112 to 156, wherein the number of adverse events during the administration of the sustained release biodegradable ocular implant is low.

158.The method of claim 157, wherein the number of treatment-related ocular adverse events during the administration of the sustained release biodegradable ocular implant is low.

159.A method of manufacturing a sustained release biodegradable ocular implant comprising a hydrogel and an active agent according to any of claims 1 to 111, the method comprising the steps of forming a hydrogel comprising a polymer network and active agent particles dispersed in the hydrogel, shaping the hydrogel and drying the hydrogel.

160.The method of claim 159, wherein the active agent is selected from immunosuppressants, complement protein C5 agents (e.g., eculizumab or avacincaptad pegol), steroids, anti-inflammatories such as steroidal and non-steroidal anti-inflammatories (e.g., COX1 or COX 2 inhibitors), antivirals, antibiotics, anti-glaucoma agents, anti-VEGF agents, analgesics .

161.The method of claim 159 or 160, wherein the active agent particles are micronized and/or homogeneously dispersed within the hydrogel.

162.The method of any of claims 159 to 161, wherein the polymer network is formed by crosslinking multi-arm polyethylene glycol units in a buffered solution.

163.The method of any of claims 159 to 162, wherein the hydrogel comprises a polymer network that is formed by mixing and reacting an electrophilic group-containing multi-arm polyethylene glycol with a nucleophilic group-containing multi-arm polyethylene glycol in a buffered solution in the presence of the tyrosine kinase inhibitor, and allowing the mixture to gel.

164.The method of claim 163, comprising reacting 4a20kPEG-SAZ with 8a20kPEG-NH_2 in a weight ratio of about 2:1.

165.The method of claim 163 or 164, wherein the method comprises the steps of filling the mixture into a mold or tubing prior to complete gelling in order to provide the desired final shape of the hydrogel, allowing the mixture to gel, and drying the hydrogel.

166.The method of claim 165, wherein the mixture is filled into a fine diameter tubing in order to prepare a hydrogel fiber.

167.The method of claim 166, wherein the inside of the tubing has a round geometry.

168.The method of claim 166, wherein the inside of the tubing has a non-round geometry.

169.The method of claim 168, wherein the inside of the tubing has a cross-shaped geometry.

170.The method of any of claims 166 to 169, wherein the method further comprises stretching the fiber and/or twisting the fiber.

171.The method of claim 170, wherein the stretching is performed prior to or after drying the hydrogel.

172.The method of claim 171, wherein the fiber is stretched by a stretch factor of about 1 to about 4.5.

173.The method of claim 171, wherein the stretching is performed after drying the hydrogel by a stretch factor of about 2 to about 5 or a stretch factor of about 3 to about 4.5.

174.The method of claim 171, wherein the stretching is performed in a wet state prior to drying the hydrogel at a stretch factor of about 0.5 to about 5, or a stretch factor of about 1 to about 4, or a stretch factor of about 1.3 to about 3.5, or a stretch factor of about 1.7 to about 3.

175.The method of any of claims 159 to 174, wherein the method further comprises loading the implant in a dried state into a needle.

176.The method of claim 175, wherein the needle is a 25- or 27-gauge needle.

177.A method of imparting shape memory to a hydrogel fiber comprising an active agent dispersed in the hydrogel by stretching the hydrogel fiber in the longitudinal direction.

178.A method of manufacturing an ocular implant comprising a hydrogel comprising an active agent dispersed therein, wherein the implant changes its dimensions upon administration to the eye, the

method comprising preparing a fiber of the hydrogel and stretching the fiber in the longitudinal direction.

179.The method of claim 177 or 178, wherein the method comprises the step of drying the hydrogel, wherein the fiber is stretched in the longitudinal direction prior to or after said drying (wet or dry stretching).

180.The method of any of claims 177 to 179, wherein the fiber is stretched by a factor of about 0.5 to about 5, or a factor of about 1 to about 4.5, or a factor of about 3 to about 4.5 or a factor of about 1 to about 2.

181.The method of any of claims 177 to 180, wherein the active agent is selected from immunosuppressants, complement protein C5 agents (e.g., eculizumab or avacincaptad pegol), steroids, anti-inflammatories such as steroidal and non-steroidal anti-inflammatories (e.g., COX1 or COX 2 inhibitors), antivirals, antibiotics, anti-glaucoma agents, anti-VEGF agents, analgesics.

182.The method of any of claims 177 to 181, wherein the hydrogel comprises a polymer network comprising crosslinked polyethylene glycol units.

183.The method of any of claims 177 to 182, wherein the fiber upon hydration fully or partly returns to approximately its original length and/or original diameter that it had prior to the stretching.

184.The method of any of claims 177 to 183, wherein the change in dimensions is an increase in diameter, or an increase in diameter together with a decrease in length.

185.A kit comprising one or more sustained release biodegradable ocular implant(s) according to any of claims 1 to 111 or manufactured in accordance with the method of any of claims 159 to 176 and one or more needle(s), wherein the one or more needle(s) is/are each pre-loaded with one sustained release biodegradable ocular implant in a dried state.

186.The kit of claim 185, wherein the needle(s) is/are 25- or 27-gauge needle(s).

187.The kit of claim 185 or 186, wherein the kit comprises one or more 25- or 27-gauge needle(s) each loaded with an implant.

188.The kit of claim 187, wherein the implant contains an active agent selected from immunosuppressants, complement protein C5 agents (e.g., eculizumab or avacincaptad pegol), steroids, anti-inflammatories such as steroidal and non-steroidal anti-inflammatories (e.g., COX1 or COX 2 inhibitors), antivirals, antibiotics, anti-glaucoma agents, anti-VEGF agents, analgesics.

189.The kit of claim 185 or 186, wherein the kit comprises one 25-gauge or 27--gauge needle loaded with an implant.

190.The kit of claim 189, wherein the implant contains an anti-biotic.

191.The kit of any of claims 185 to 190, further containing an injection device for injecting the implant into the eye of a patient.

192.The kit of claim 191, wherein the injection device is provided in the kit separately from the one or more needle(s) loaded with implant.

193.The kit of claim 191, wherein the injection device is pre-connected to a needle loaded with implant.

194.The kit of claim 191 or 192, wherein the injection device contains a push wire to deploy the implant from the needle into the eye.

195.The kit of any of claims 185 to 194, further comprising one dose of an anti-VEGF agent ready for injection.

196.An injection device suitable for injecting a sustained release biodegradable ocular implant according to any of claims 1 to 111 into the eye.

197.The injection device of claim 196 containing means for connecting the injection device to a needle,

~~198.The injection device of claim 196 or 197, wherein the needle is pre-loaded with the implant.~~

~~199.The injection device of any of claims 196 to 198 containing a push wire to deploy the implant from the needle into the eye when the injection device has been connected to the needle.~~

~~200.The injection device of claim 199, wherein the push wire is made of Nitinol or stainless steel/Teflon.~~

~~201.The injection device of claim 199 or 200, obtainable by affixing the wire to the plunger and encasing it between two snap fit injector body parts and securing the plunger with a clip.~~

~~202.A pharmaceutical product comprising the sustained release biodegradable ocular implant of any of claims 1 to 111 loaded in a needle and an injection device according to any of claims 196 to 201, wherein the needle is pre-connected to the injection device.~~

~~203.A sustained release biodegradable ocular implant according to any of claims 1 to 111 for use in treating an ocular disease in a patient in need thereof according to any of claims 112 to 138 or in treating neovascular age-related macular degeneration in a patient in need thereof according to any of claims 139 to 158.~~

~~204.~~16. Use of a sustained release biodegradable ocular implant according to any of claims 1 to 14 ~~1 to 111~~ in the preparation of a medicament for the treatment of ~~an ocular disease in a patient in need thereof according to any of claims 112 to 138 or for the treatment of~~ neovascular age-related macular degeneration ~~in a patient in need thereof according to any of claims 139 to 158~~.

~~205.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, the method comprising administering to the patient the sustained release biodegradable ocular implant containing an active agent according to any of claims 1 to 111.~~

~~206.The method of claim 205, wherein the ocular disease is neovascular age-related macular degeneration.~~

~~207.The method of claim 205 or 206, wherein the central subfield thickness is reduced in the patient during a period of at least 3 months, at least 6 months, at least 9 months, at least 11 months, or at least 12 months after administration of the implant with respect to a baseline central subfield thickness measured in that patient prior to the administration of the implant.~~

~~208.A sustained release biodegradable ocular implant according to any of claims 1 to 111 for use in 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 according to any of claims 205 to 207.~~

~~209.Use of a sustained release biodegradable ocular implant according to any of claims 1 to 111 in the preparation of a medicament for 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 according to any of claims 205 to 207.~~