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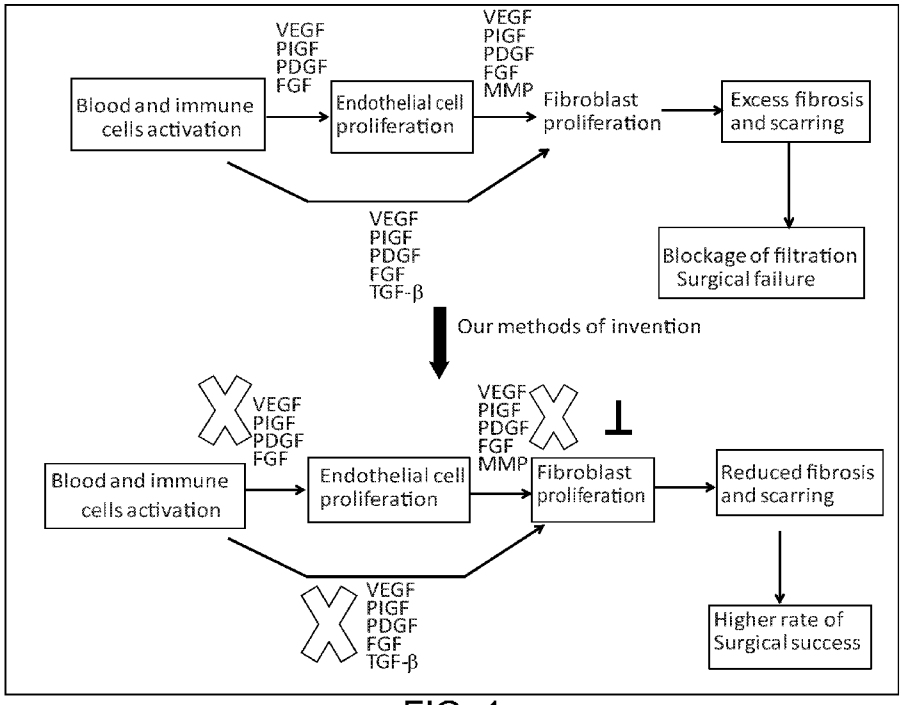

FIG. 1

(57) Abstract: Compositions and methods of using nintedanib for improving the success rate of glaucoma filtration surgery are disclosed herein. Nintedanib can be used alone or in combination with an anti-metabolite drug in a topical or implant eye formulation.

[Continued on next page]

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COMPOSITIONS AND METHODS OF USING NINTEDANIB FOR IMPROVING GLAUCOMA SURGERY SUCCESS

CLAIM OF PRIORITY

This application claims the benefit of U.S. Provisional Patent Application Serial No. 62/344,878, filed on June 02, 2016, and U.S. Provisional Patent Application Serial No. 62/344,870, filed on June 02, 2016, the entire contents of each are hereby incorporated by reference.

TECHNICAL FIELD

The present disclosure relates to ocular compositions comprising nintedanib and methods of use thereof for improving the success rate of glaucoma surgery.

BACKGROUND

Glaucoma refers to a group of eye conditions that damage the optic nerve, which is often caused by an abnormally high pressure in the eye. One way to reduce pressure in an eye with glaucoma is to surgically create a drain in the eye. This type of surgery is called a glaucoma filtration surgery, e.g., trabeculectomy. In glaucoma surgery, a piece of tissue in the drainage angle of the eye is removed, creating an opening. This new opening creates a drain, allowing fluid to drain out of the eye. The eye pressure is reduced because fluid can now drain with relative ease through the new opening through the new opening into a reservoir (bleb) underneath the conjunctiva. The fluid is then absorbed by the body.

As a result of glaucoma filtration surgery, scarring and fibrosis can develop at the surgical site. The scarring and fibrosis often results in a gradual reduction of filtration and loss of control of intraocular pressure. Excess fibrosis is a key factor leading to scar formation and the failure of glaucoma filtration surgery. Current treatments for reducing the failure are still inadequate and need improvements.

SUMMARY

In certain aspects, the disclosure provides a method for improving the success rate of glaucoma surgery (e.g., glaucoma filtration surgery) by administering nintedanib to the eye of a subject in need of such treatment. One aspect features a

method for adjunctive treatment associated with glaucoma filtration surgery in a subject comprising administering to a subject in need thereof an effective amount of a composition comprising nintedanib or a pharmaceutically acceptable salt thereof. The method improves the success rate of glaucoma surgery. Glaucoma surgery includes, for example, the classic trabeculectomy method, or a method selected from the group consisting of Trabectome, Gonioscopy-assisted transluminal trabeculectomy, Excimer laser trabeculostomy, and Endoscopic cyclophotocoagulation. The glaucoma surgery performed may also be for implantation of an ocular filtration device, wherein the ocular filtration device is an ocular stent. For example, the ocular filtration device may be selected from the group consisting of an iStent, Hydrus and CyPass microstent.

In some aspects of the methods disclosed herein, the amount of nintedanib administered to the subject is effective to extend the duration of lower IOP, increase either the absolute success rate or the qualified success rate for at least 10 days, at least 90 days, at least 365 days, at least 750 days, or at least 3650 days following surgery; or wherein the amount of nintedanib administered is effective to prolong bleb survival.

In some aspects, the nintedanib composition is administered in the form of topical ocular formulation (e.g., a topical eye drop) or implant. In some examples, the nintedanib is in a topical ocular formulation administered topically to the affected eye. In certain aspect, the concentration of nintedanib in the formulation is from 0.001% to 10% by weight or by volume the total amount of composition. In certain aspect, the topical ocular formulation is a solution, a suspension or an emulsion. In another aspect, nintedanib is in an implant or semi-solid sustained release formulation injected into the affected eye. In certain aspect, the amount of nintedanib in the implant is from 1 μg to 100 mg.

In certain aspect, the disclosed methods are performed by the combination of nintedanib and an antimetabolite drug. The antimetabolite drug can be, but not limited to, Mitomycin C, 5-Fluorouracil, Floxuridine, Cytarabine, 6-Azauracil, Azathioprine, Methotrexate, Mycophenolate Mofetil, and Thiotepa.

In another aspect, the disclosed methods reduce scar formation in glaucoma surgery by attenuating abnormal vascularity and fibrosis at the surgical site. In certain aspect, the disclosed methods are performed before operation, in conjunction with operation or after operation, to reduce failure in glaucoma surgery. Thus, in some

aspects, the amount of nintedanib administered is effective to reduce scar formation at the site of the surgery; In some aspects, the amount nintedanib administered is effective to extend the duration of lower IOP for at least 10 days, at least 365 days, or at least 3650 days following surgery. In some aspects, the amount of nintedanib administered is effective to prolong bleb survival

As used herein, the term "one or more" includes at least one, more suitably, one, two, three, four, five, ten, twenty, fifty, one-hundred, five-hundred, etc., of the item to which "one or more" refers

The term "subject" refers to an animal or human, or to one or more cells derived from an animal or human. Preferably, the subject is a human. Subjects can also include non-human primates. A human subject can be known as a patient.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Methods and materials are described herein for use in the present invention; other suitable methods and materials known in the art can also be used. The materials, methods, and examples are illustrative only and not intended to be limiting. All publications, patent applications, patents, sequences, database entries, and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present specification, including definitions, will control.

Other features and advantages of the invention will be apparent from the following detailed description and figures, and from the claims.

DESCRIPTION OF DRAWINGS

Figure 1 is a flow chart demonstrating an exemplary mechanism to reduce excess scar formation and to improve the success rate of glaucoma surgery.

Figure 2 is a graph showing bleb survival following glaucoma filtration surgery in a rabbit model.

Figure 3 is a graph showing intraocular pressure (IOP) following glaucoma filtration surgery in a rabbit model.

Figure 4 is a graph showing absolute success of glaucoma filtration surgery in a clinical study according to the methods disclosed herein.

DETAILED DESCRIPTION

Glaucoma is a group of diseases that are characterized by the death of retinal ganglion cells ("RGCs"), specific visual field loss, and optic nerve atrophy. Glaucoma is a leading cause of blindness in the world. A variety of treatment options, effective to reduce intraocular pressure ("IOP"), are available to control, and, perhaps, to slow, the progression of the disease. Treatment options include, for example, pharmaceutical therapy (i.e., IOP-lowering drugs), laser eye surgery, and/or conventional surgical methods, such as glaucoma filtration surgery (or also known as filtering surgery or trabeculectomy).

Despite the wide usage of topical IOP-lowering drugs in the developed countries, glaucoma surgery is still commonly practiced in other parts of the world, especially for closed-angle glaucoma. Glaucoma surgery has the advantage of low cost over time and doesn't have to deal with compliance issues associated with topical eye drops that need multiple applications per day. The traditional glaucoma filtration surgery and trabeculectomy have high failure rate (Schlunck et al. Exp Eye Res. 2016; 142:76-82) and methods of implanting an ocular filtration device, e.g., a glaucoma drainage device, also have long term failure problems (Amoozgar et al. Curr Opin Ophthalmol. 2016;27(2):164-9). The failures are due to excessive postoperative wound healing with subsequent fibrosis and scar formation that obstruct drainage. The damage to tissue by surgery often induces pro-inflammation and pro-fibrogenic factors that lead to abnormal extracellular matrix change and fibrosis. Myofibroblast hyper-proliferation induced by these factors subsequently causes excessive fibrosis and scar formation.

The antimetabolite drug, Mitomycin C (MMC) has been administered during or after glaucoma surgery as an anti-scaring agent. Another antimetabolite drug, 5-fluorouracil (5-FU), is also used mainly by local injection during follow-up (Schlunck et al. Exp Eye Res. 2016; 142:76-82). These antimetabolite drugs work by blocking fast proliferating fibroblasts. Their activities are not selective and are known to cause side effects. For example, the anti-cell division activity sometimes causes bleb leakage post-surgery. Better postoperative management of glaucoma surgery is still an unmet medical need.

Due to the multi-factorial causes of scar formation following glaucoma surgery, targeting any single pathway alone may not be sufficient to improve surgery success. The present disclosure improves glaucoma surgery success by administering to the eye a composition with the following key attributes: 1) the composition will

inhibit several important pathological pathways simultaneously and these pathways are disclosed below; 2) the composition utilizes small molecule drug(s) as opposed to antibody drugs to achieve more efficient drug delivery to the target tissue; 3) the composition is a topical formulation in the form of either an eye drop or implant for convenient and consistent drug delivery to the site of surgery; and 4) the composition contains nintedanib, which can be used in combination with an antimetabolite drug to achieve additive or synergistic effect in improving the success of glaucoma filtration surgery.

The disclosure provides a method of using a topical formulation (e.g., topical eye drop, implant) comprising nintedanib, before, during or after surgery. Nintedanib meets the requirement of inhibiting vascular endothelial growth factor ("VEGF") receptors ("VEGFR") 1-3, platelet-derived growth factor receptor ("PDGFR") -α and -β and fibroblast growth factor receptor 2 ("FGFR2") to achieve the needed efficacy.

Without being bound to theory, it is understood that it is important to inhibit all VEGFR members is critical because of the need to block placental growth factor ("PIGF") in addition to VEGF. PIGF only acts on pathologic angiogenesis and inflammation and contributes more to the problems associated with glaucoma surgery (Van Bergen et al. J Cell Mol Med. 2013; 17(12):1632-43). For glaucoma filtration surgery, the disclosed methods also inhibit FGFR2 due to its function in scar formation. The topical formulation disclosed herein allows for convenient treatment before, during and after surgery. The mechanism for improving glaucoma surgery success rate provided by the present disclosure is summarized in Figure 1, which shows that nintedanib, in a suitable ocular formulation, would simultaneously block signal pathways of the key pathogenic factors involved in excess wound healing, including PIGF, VEGF, PDGF, FGF, and would enhance the success of glaucoma surgery by reducing scar formation.

As used herein, the term "improving glaucoma surgery success" means extending the duration of reduced (i.e., lower) IOP for a period of at least 10 days, at least 90 days, at least 365 days, at least 750 days, or at least 3650 days) following surgery, an increase of IOP-reduction percentage comparing to the pre-surgical baseline over a given period of time (e.g., at least 10 days, at least 90 days, at least 365 days, at least 750 days, or at least 3650 days) after surgery, increase of the absolute (also known as complete) success rate (defined as percent of patients kept

within normal IOP range with reduced IOP in relation to the baseline without any glaucoma medication) over a given period of time, increase of qualified success rate (defined as percent of patients kept within normal IOP range with reduced IOP in relation to the baseline with the help of glaucoma medications) over certain period of time (e.g., at least 10 days, at least 90 days, at least 365 days, at least 750 days, or at least 3650 days), improvement of the bleb grade and survival over certain period of time (e.g., at least 10 days, at least 90 days, at least 365 days, at least 750 days, or at least 3650 days).

As used herein, "normal IOP" or "normal IOP range" refers to intraocular pressure in the human eye of between about 5 mm Hg to about 22 mm Hg, or about 10 mm Hg to about 21 mm Hg.

The terms "treatment", "treating", "treat" and the like are used herein to generally refer to obtaining a desired pharmacologic and/or physiologic effect. The effect can be prophylactic in terms of completely or partially preventing a disease or symptom(s) thereof and/or may be therapeutic in terms of a partial or complete stabilization or cure for a disease and/or adverse effect attributable to the disease. The term "treatment" encompasses any treatment of a disease in a mammal, particularly a human, and includes: (a) preventing the disease and/or symptom(s) from occurring in a subject who may be predisposed to the disease or symptom but has not yet been diagnosed as having it; (b) inhibiting the disease and/or symptom(s), i.e., arresting their development; or (c) relieving the disease symptom(s), i.e., causing regression of the disease and/or symptom(s). Those in need of treatment include those already inflicted (e.g., those with high IOP, those with an infection, etc.) as well as those in which prevention is desired (e.g., those with increased susceptibility to glaucoma, those suspected of having high IOP, etc.).

Nintedanib {Methyl (3Z)-3-{[(4-{methyl[(4-methylpiperazin-1-yl) acetyl] amino}phenyl)amino] (phenyl)methylidene}-2-oxo-2,3-dihydro-1H-indole-6-carboxylate}is a kinase inhibitor as described herein. Nintedanib inhibits primarily receptor tyrosine kinases including, for example vascular endothelial growth factor receptor (VEGFR 1-3), platelet-derived growth factor receptor (PDGFR α and β), fibroblast growth factor receptor (FGFR 1-4).

Formulations and Dosing Regimen

The methods described herein include the manufacture and use of pharmaceutical compositions, which include compounds identified by a method described herein as active ingredients. Also included are the pharmaceutical compositions themselves.

Pharmaceutical compositions typically include pharmaceutically acceptable excipients. As used herein the language “pharmaceutically acceptable excipient” or “pharmaceutically acceptable carrier” includes saline, solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like, compatible with pharmaceutical administration.

The phrase "pharmaceutically acceptable salt" as used herein means those salts of a compound of interest that are safe and effective for administration to a mammal and that possess the desired biological activity. Pharmaceutically acceptable acid salts include, but are not limited to hydrochloride, hydrobromide, hydroiodide, nitrate, sulfate, bisulfate, phosphate, acid phosphate, I 0 isonicotinate, carbonate, bicarbonate, acetate, lactate, salicylate, citrate, tartrate, propionate, butyrate, pyruvate, oxalate, malonate, pantothenate, bitartarte, ascorbate, succinate, maleate, gentisinate, fumarate, gluconate, glucaronate, saccharate, formate, benzoate, glutamate, methanesulfonate, thanesulfonate, benzenesulfonate, p-toluenesulfonate and pamoate (i.e., I, I'rnethylene-bis-(2-hydroxy-3-naphthoate)) salts. Suitable base salts include, but are not limited to, 15 aluminum, calcium, lithium, magnesium, potassium, sodium, zinc, bismuth, and diethanolamine salts.

Methods of formulating suitable pharmaceutical compositions are known in the art, see, e.g., Remington: The Science and Practice of Pharmacy, 21st ed., 2005; and the books in the series Drugs and the Pharmaceutical Sciences: a Series of Textbooks and Monographs (Dekker, NY). For example, solutions, suspensions, , creams, ointments, Gels, gel-forming liquid, suspension containing liposomes or micelles, spray orformulation, or emulsions used for ophthalmic application can include the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerin, propylene glycol or other synthetic solvents; antibacterial agents; antioxidants; chelating agents; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose. The pH can be adjusted with acids or bases, such as hydrochloric acid or sodium hydroxide.

Pharmaceutical compositions suitable for injectable use can include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. It should be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyetheylene glycol, and the like), and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Prevention of the action of microorganisms can be achieved by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, ascorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as mannitol, sorbitol, and sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent that delays absorption, for example, aluminum monostearate and gelatin.

Sterile injectable solutions can be prepared by incorporating the active compound in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the active compound into a sterile vehicle, which contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and freeze-drying, which yield a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

In one embodiment, the therapeutic compounds are prepared with carriers that will protect the therapeutic compounds against rapid elimination from the body, such as a controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Such formulations can be prepared using standard techniques, or obtained commercially.

The pharmaceutical compositions can be included in a container, pack, or dispenser together with instructions for administration.

Compositions and formulations of nintedanib, can be administered topically (e.g., as a topical ocular formulation) or as an injection of semi-solid formulation or solid implant, or by any other suitable methods known in the art. While it is possible to use the agent disclosed herein for therapy as is, it may be preferable to administer the agent as a pharmaceutical formulation, e.g., in admixture with a suitable pharmaceutical excipient, diluent, or carrier selected with regard to the intended route of administration and standard pharmaceutical practice. Pharmaceutical formulations include at least one active compound, in association with a pharmaceutically acceptable excipient, diluent, and/or carrier.

The pharmaceutical composition disclosed herein may include a "therapeutically effective amount" of an agent described herein. Such effective amounts can be determined based on the effect of the administered agent, or the combinatorial effect of agents if more than one agent is used. A therapeutically effective amount of an agent may also vary according to factors such as the disease state, age, sex, and weight of the individual, and the ability of the compound to elicit a desired response in the individual, e.g., amelioration of at least one disorder parameter or amelioration of at least one symptom of the disorder. A therapeutically effective amount is also one in which any toxic or detrimental effects of the composition are outweighed by the therapeutically beneficial effects.

Effective doses of the compositions of the present disclosure, for the treatment of conditions vary depending upon many different factors, including means of administration, target site, physiological state of the subject, whether the subject is human or an animal, other medications administered, and whether treatment is prophylactic or therapeutic. Treatment dosages can be titrated using routine methods known to those of skill in the art to optimize safety and efficacy.

In some instances, the topical ocular formulation is a solution, a suspension, , creams, ointments, gels, gel-forming liquid, suspension containing liposomes or micelles, spray formulation, or an emulsion. In some cases, the topical ocular formulation also includes one or more pharmaceutically acceptable excipients selected from stabilizers, surfactants, polymer base carriers, gelling agents, organic co-solvents, pH active components, osmotic active components and with or without preservatives. In some cases, the sustained release semi-solid formulation, sustained

release solid formulation or ocular implant is injected into the affected eye. In some embodiments, the sustained release semi-solid formulation, sustained release solid formulation or ocular implant further comprises a pharmaceutically acceptable excipient. In some cases, the sustained release semi-solid formulation, sustained release solid formulation or ocular implant includes a multikinase inhibitor, the antimetabolite, or combination thereof; and a biodegradable polymer selected from polylactic acid (PLA), polyglycolic acid (PLGA) and polylactic acid polyglycolic acid copolymers.

Administration of a composition or formulation can be once a day, twice a day, three times a day, four times a day or more often. Frequency may be decreased during a treatment maintenance phase of the treatment, e.g., once every second or third day instead of every day or twice a day. The dose and the administration frequency can be adjusted based on the judgment of the treating physician, for example, taking into account the clinical signs, pathological signs and clinical and subclinical symptoms of a disease of the conditions treated with the present methods, as well as the patient's clinical history.

It will be appreciated that the amount of an agent disclosed herein required for use in treatment will vary with the route of administration, the nature of the condition for which treatment is required, and the age, body weight and condition of the patient, and will be ultimately at the discretion of the attendant physician. Compositions will typically contain an effective amount of nintedanib. Preliminary doses can be determined according to animal tests, and the scaling of dosages for human administration can be performed according to art-accepted practices.

Length of treatment, i.e., number of days, will be readily determined by a physician treating the subject; however, the number of days of treatment may range from about 1 day to about 365 days. As provided by the present methods, the efficacy of treatment can be monitored during the course of treatment to determine whether the treatment has been successful, or whether additional (or modified) treatment is necessary.

Dosage, toxicity and therapeutic efficacy of the therapeutic compounds can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., for determining the LD50 (the dose lethal to 50% of the population) and the ED50 (the dose therapeutically effective in 50% of the population). Dosage forms for nintedanib can be readily determined by the ordinarily skilled artisan, and can e.g.,

be obtained in animal models and in clinical studies reported in the literatures, for determining dosage, safety and efficacy according to standard methods known in the art. The exact formulation, route of administration and dosage can be chosen by the individual physician in view of the patient's condition.

Compositions for use in the present methods may include nintedanib at a concentration of 0.001% to 10% by weight or by volume the total amount of composition. For example, an aqueous composition comprises 0.001%, 0.01%, 0.1%, 0.5%, 1.0%, 1.5%, 2.0%, 5.0% or up to 10% nintedanib.

As will be familiar to those skilled in the art, administration to the eye of an aqueous solution may be in the form of "drop" or number of drops (e.g. of nintedanib solution) from a dropper or pipette or other dedicated sterile devices. Such drops will typically be up to 50 microliters in volume, but maybe smaller e.g. less than 10 microliters.

EXAMPLES

The invention is further described in the following examples, which do not limit the scope of the invention described in the claims.

Example 1: Rabbit Glaucoma Surgery Model.

The rabbit glaucoma surgery model is used to illustrate use of the presently disclosed methods for improving the success of glaucoma filtration surgery. Specially, an established rabbit model of glaucoma filtration surgery would be used to study the effects of nintedanib 0.2% solution on the wound-healing events after surgery. The surgical procedure is as described in Wong et al. (Wong et al. Invest Ophthalmol Vis Sci. 2003; 44(3):1097-1103). Briefly, a partial thickness 8-0 silk corneal traction suture is placed superiorly, and the eye pulled down. A fornix based conjunctival flap is raised, after which a blunt dissection of the subconjunctival space is performed of approximately 5 mm along the limbus and 8 mm posteriorly. A microvitreoretinal (MVR) blade is used to make a partial-thickness scleral incision 3 to 4 mm behind the limbus, and a scleral tunnel to the corneal stroma is fashioned. A 22-gauge, 25-mm intravenous cannula (Venflon 2; Beckton Dickinson, Oxford, UK) is passed through a scleral tunnel anteriorly until the cannula needle is visible in the clear cornea. Entry into the anterior chamber is made with a cannular needle, which is then withdrawn as the cannula is advanced to the mid-pupillary area. The cannula is trimmed and

beveled at its scleral end so that it protrudes 1 mm from the insertion point, and a 10-0 nylon suture is placed to fix the tube to the scleral surface. The conjunctival incision is closed with two interrupted sutures and a central, mattress-type 10-0 nylon suture attached to a needle (B/V 100-4; Ethicon) to give a water-tight closure. One drop each of guttae chloramphenicol and Betnesol-N (Glaxo Wellcome, Uxbridge, UK) ointment is instilled at the end of surgery.

Twenty female New Zealand White rabbits (2–2.4 kg, 12–14 weeks old; Charles River) would be acclimatized for 5 days before the experiments start. Glaucoma surgery would be performed on the left eye as described. After surgery, the rabbits would be arranged into two groups and one group would be treated with vehicle and another with nintedanib 0.2% solution. Treatments would begin immediately after surgery and the treatment would be TID for 2 weeks. The survival of the bleb formed by the surgery and the intraocular pressure (IOP) would be followed for 28 days. Histological analysis of the scar tissue would be performed at the end of the study.

Results

Surgery success outcome would be significantly prolonged in the nintedanib group compared with the vehicle group. Figure 2 provides a graph showing the survival curve of the bleb after surgery. As shown in Figure 2, the nintedanib group would show a substantially prolonged bleb survival comparing to the vehicle group. By the end of study on day 28, no bleb would survive in the vehicle group while most of the bleb would survive in the nintedanib group. Figure 3 is a graph showing the IOP curve during the follow up period after the surgery. IOP remained low (i.e., below 20 mm Hg) in the nintedanib group and increased gradually in the vehicle group. The difference would be statistically significant. In addition to bleb survival and IOP change, histological analysis of scar tissue at the surgical site would show less scar tissue in the nintedanib group than the vehicle group.

The results from this experiment would indicate that the nintedanib 0.2% solution increases the success of glaucoma surgery (i.e., prolonged bleb survival, extended duration of lower IOP following surgery and/or reduced fibrosis/scarring).

Example 2: **Topical Ocular Formulations of Nintedanib as Adjunct Therapy to Glaucoma Filtration Surgery**

Topical nintedanib 0.2% as adjunct therapy to increase success of trabeculectomy in a clinical study. A randomized, double-masked, placebo-controlled, 12-month experimental trial to test the effects of topical nintedanib 0.2% on the success rate of trabeculectomy. The study design would be as described by Vandewalle et al (Vandewalle et al. Br J Ophthalmol. 2014, Jan; 98(1):73-8).

Patients with medically uncontrolled open-angle glaucoma scheduled for a primary trabeculectomy would be enrolled and randomized to receive one drop TID of either nintedanib or placebo solutions. The treatment would start immediately after surgery and would last for a month. Approximately 150 patients would be enrolled in the study.

Surgeries would be performed under general or retrobulbar anaesthesia by experienced surgeons using a modified Moorfields technique. IOP would be measured by Goldmann applanation tonometry. Two measurements were taken by masked observers and averaged to determine the mean IOP if two values were within 2 mm Hg. A third measurement would be taken if the difference between the first two determinations is >2 mm Hg.

Patients would be examined on day 1; at weeks 1, 2, and 4; and at months 3, 6, and 12 after trabeculectomy. All patients would go through a comprehensive ophthalmic examination that included measurements of best-corrected visual acuity, slit-lamp examination including a Seidel test, IOP measurement, and fundus biomicroscopy with a 90-diopter lens. The number of postoperative IOP-lowering medications, intra- and postoperative complications, and surgical interventions would also be recorded.

Absolute success would be the primary endpoint and is defined as intraocular pressure (IOP) ≤21 mm Hg and >5 mm Hg with at least 20% reduction from baseline and no loss of light perception.

Results

IOP would be effectively reduced in both nintedanib and placebo groups at the 12-month visit when compared to baseline. The absolute success rate of glaucoma surgery, i.e., maintaining IOP of less than about 20 mm Hg for more than 12 months after surgery, would be higher in the nintedanib group vs the placebo group as shown in Figure 4. At time points after 6 months, the differences would be statistically significant.

Example 3: Formulations

Nintedanib Ophthalmic Solution

The drug product is an isotonic ophthalmic solution prepared in 2-hydroxypropyl beta cyclodextrin or other similar cyclodextrins, and buffer solution, pH range from 5.5 to 8.0. Other viscosity, lubricant, preservative agents might be added to enhance functionality of the formulation. The compositions of the ophthalmic solution are disclosed in Table 1.

Table 1 Nintedanib Ophthalmic Solution

Ingredients	**Functions**	**Concentration Range (%w/v)**
CBT-001 (Nintedanib free base)	Active Pharmaceutical Ingredient	0.001 – 10
Sodium carboxymethylcellulose	Viscosity Agent/dry eye relief	0 – 1
Pemulen TR	Viscosity Agent	0 – 0.2
Polyvinyl alcohol	Viscosity/Lubrication Agent	0 – 1.5
Hypromellose	Lubricant/dry eye relief	0 - 1
Carbomers	Lubricant/dry eye relief	0 – 0.5
Carmellose sodium	Lubricant/dry eye relief	0 – 1
Sodium hyaluronate	Lubricant/dry eye relief	0 – 1.5
Polyethylene glycol 400	Lubricant/dry eye relief	0 – 0.4
Propylene glycol	Lubricant/dry eye relief	0 – 0.6
2-hydroxypropyl beta cyclodextrin	Solubilizer	0 - 10
Sulfobutyl-beta-cyclodextrin	Solubilizer	0 - 10
Randomly methylated beta-cyclodextrin	Solubilizer	0 – 5
α-cyclodextrin	Solubilizer	0 - 4
β-cyclodextrin	Solubilizer	0 - 1
γ-cyclodextrin	Solubilizer	0 - 1
Poloxamer 188, or 237, or 407	Solubilizer/lubricant	0 – 5
Polysorbate 80	Solubilizer/lubricant/surfactant	0 – 1
Edetate disodium	Chelating Agent/Preservative	0 – 0.01
Benzalkonium chloride	Preservative	0 – 0.02

Ingredients	Functions	Concentration Range (%w/v)
Sodium phosphate monobasic monohydrate	Buffer Agent	0 – 0.43
Sodium phosphate dibasic heptahydrate	Buffer Agent	0 – 0.8
Boric acid	Buffer Agent	0 – 0.6
Sodium borate, decahydrate	Buffer Agent	0 – 0.045
Citric acid, monohydrate	Buffer Agent/preservative	0 – 0.13
Sodium citrate, dihydrate	Buffer Agent/preservative	0 – 0.45
Glycerin	Tonicity Agent	0 – 2.2
Sodium chloride	Tonicity Agent	0 – 0.83
1N Sodium hydroxide	pH Adjustment	pH 5.5 – 8.0
1N Hydrochloric acid		
Water for injection	Vehicle	Q.S. to 100

Nintedanib Ophthalmic Suspension

The drug product is an isotonic ophthalmic suspension prepared in carboxymethylcellulose sodium and buffer solution, pH range from 5.5 to 8.0. The drug particle sizes are reduced to below 40 micron. Other viscosity, lubricant, solubilizer, and preservative agents might be added to enhance functionality of the formulation suspension. The compositions are disclosed in Table 2.

Table 2 Nintedanib Ophthalmic Suspension

Ingredients	Functions	Concentration Range (%w/v)
CBT-001 (Nintedanib free base)	Active Pharmaceutical Ingredient	0.001 – 10
Sodium carboxymethylcellulose	Viscosity Agent/dry eye relief	0 – 1
Pemulen TR	Viscosity Agent	0 – 0.2

Ingredients	Functions	Concentration Range (%w/v)
Polyvinyl alcohol	Viscosity/Lubrication Agent	0 – 1.5
Hypromellose	Lubricant/dry eye relief	0 - 1
Carbomers	Lubricant/dry eye relief	0 – 0.5
Carmellose sodium	Lubricant/dry eye relief	0 – 1
Sodium hyaluronate	Lubricant/dry eye relief	0 – 1.5
Polyethylene glycol 400	Lubricant/dry eye relief	0 – 0.4
Propylene glycol	Lubricant/dry eye relief	0 – 0.6
2-hydroxypropyl beta cyclodextrin	Solubilizer	0 - 10
Sulfobutyl-beta-cyclodextrin	Solubilizer	0 - 10
Randomly methylated beta-cyclodextrin	Solubilizer	0 – 5
α-cyclodextrin	Solubilizer	0 - 4
β-cyclodextrin	Solubilizer	0 - 1
γ-cyclodextrin	Solubilizer	0 - 1
Poloxamer 188, or 237, or 407	Solubilizer/lubricant	0 – 5
Polysorbate 80	Solubilizer/lubricant/surfactant	0 – 1
Edetate disodium	Chelating Agent/Preservative	0 – 0.01
Benzalkonium chloride	Preservative	0 – 0.02
Sodium phosphate monobasic monohydrate	Buffer Agent	0 – 0.43
Sodium phosphate dibasic heptahydrate	Buffer Agent	0 – 0.8
Boric acid	Buffer Agent	0 – 0.6
Sodium borate, decahydrate	Buffer Agent	0 – 0.045
Citric acid, monohydrate	Buffer Agent/preservative	0 – 0.13
Sodium citrate, dihydrate	Buffer Agent/preservative	0 – 0.45
Glycerin	Tonicity Agent	0 – 2.2
Sodium chloride	Tonicity Agent	0 – 0.83
1N Sodium hydroxide	pH Adjustment	pH 5.5 – 8.0
1N Hydrochloric acid		
Water for injection	Vehicle	Q.S. to 100

Nintedanib Ophthalmic Emulsion

The drug product is an isotonic ophthalmic emulsion. The drug is dissolved in the mixture oil phase and emulsifier excipients which is then emulsified and mixed with an aqueous phase with pH range from 5.5 to 8.0. Other viscosity, lubricant, solubilizer, and preservative agents might be added to enhance functionality of the emulsion formulation. The compositions are disclosed in Table 3.

Table 3 Nintedanib Ophthalmic Emulsion

Ingredients	Functions	Concentration (% w/w)
CBT-001 (Nintedanib free base)	Active Pharmaceutical Ingredient	0.001 - 10
Castor oil	Oil solvent	0 – 1.25
Polyoxyl-40-Stearate	Emulsifier	0 – 0.25
Polysorbate 80	Solubilizer/Emulsifier/Surfactant	0 - 1
Sulfobutyl-β-cyclodextrin	Solubilizer	0 - 5
2-Hydroxypropyl-beta-cyclodextrin	Solubilizer	0 - 5
Randomly methylated beta-cyclodextrin	Solubilizer	0 – 5
α-cyclodextrin	Solubilizer	0 - 4
β-cyclodextrin	Solubilizer	0 - 1
γ-cyclodextrin	Solubilizer	0 - 1
Glycerin	Tonicity Agent	0 - 2.2
Sodium Chloride	Tonicity Agent	0 – 0.83
Pemulen TR2	Viscosity Agent	0 – 0.1
Sodium carboxymethylcellulose	Viscosity Agent	0 – 0.5
Polyvinyl alcohol	Viscosity/Lubrication Agent	0 – 1.5
Hypromellose	Lubricant/dry eye relief	0 - 1
Carbomers	Lubricant/dry eye relief	0 – 0.5
Carmellose sodium	Lubricant/dry eye relief	0 – 1
Sodium hyaluronate	Lubricant/dry eye relief	0 – 1.5
Polyethylene glycol 400	Lubricant/dry eye relief	0 – 0.4
Propylene glycol	Lubricant/dry eye relief	0 – 0.6
Poloxamer 188, or 237, or 407	Solubilizer/lubricant	0 – 5
Boric acid	Buffer	0 – 0.6
Sodium borate, decahydrate	Buffer	0 – 0.045
Citric acid, monohydrate	Buffer/preservative	0 – 0.13
Sodium citrate, dihydrate	Buffer/preservative	0 – 0.45
Sodium phosphate, monobasic monohydrate	Buffer	0 – 0.43
Sodium phosphate dibasic heptahydrate	Buffer	0 – 0.8

Ingredients	Functions	Concentration (% w/w)
1N & 5N Sodium hydroxide	pH Adjustment	pH 5.5 – 8.0
1N Hydrochloric acid		
Water for injection	Aqueous Vehicle	Q.S. 100

Nintedanib Sustained Release Semi-Solid Formulation

The drug product is an isotonic sustained release semi-solid formulation. The drug is dissolved and/or suspended in a semi-solid medium with pH range from 5.5 to 8.0. Other viscosity, lubricant, solubilizer, and preservative agents might be added to enhance functionality of the sustained release semi-solid formulation. The compositions are disclosed in Table 4.

Table 4 Sustained Release Semi-Solid Formulation

Ingredients	Functions	Concentration (% w/w)
CBT-001 (Nintedanib free base)	Active Pharmaceutical Ingredient	0.001 - 10
Xanthan Gum	Viscosity/Thickener	0 - 10
Hydroxypropyl methylcellulose	Viscosity/Thickener	0 – 10
Sodium hyaluronate	Viscosity/Thickener	0 – 5
Hyaluronic acid	Viscosity/Thickener	0 - 5
Boric acid	Buffer	0 – 0.6
Sodium borate, decahydrate	Buffer	0 – 0.045
Citric acid, monohydrate	Buffer/preservative	0 – 0.13
Sodium citrate, dihydrate	Buffer/preservative	0 – 0.45
Sodium phosphate, monobasic monohydrate	Buffer	0 – 0.43
Sodium phosphate dibasic heptahydrate	Buffer	0 – 0.8
1N & 5N Sodium hydroxide	pH Adjustment	pH 5.5 – 8.0
1N Hydrochloric acid		
Water for injection	Aqueous Vehicle	Q.S. 100

Nintedanib Sustained Release Implants

The drug product is a solid implant. The drug is mixed and blended with one or more polymers. The mixture of drug and polymers is melted at a predetermined temperature and extruded into a filament with a predetermined diameter size. The formulation filament is cut into a predetermined size of segment which can be implanted into ocular tissues. The compositions are disclosed in Table 5.

Table 5 Sustained Release Implants

Ingredients	**Functions**	**Concentration (% w/w)**
CBT-001 (Nintedanib free base)	Active Pharmaceutical Ingredient	0.001 - 10
Poly (D,L-Lactide), i.v. 0.25-0.35 dL/g	Polymer	0 – 100
Poly (D,L-Lactide-coglycolide) i.v. 0.14-0.22 dL/g	Polymer	0 – 100
Poly (D,L-Lactide), i.v. 0.16-0.25 dL/g	Polymer	0 - 100
Polyethylene Glycol 3350	Polymer	0 – 20
Resomer®RG755S	Polymer	0 - 100
Resomer®RG753H	Polymer	0 - 100

Without limitation, an example composition, for use in the methods according to the invention, may be modified from existing ophthalmically acceptable compositions.

OTHER EMBODIMENTS

It is to be understood that while the invention has been described in conjunction with the detailed description thereof, the foregoing description is intended to illustrate and not limit the scope of the invention, which is defined by the scope of the appended claims. Other aspects, advantages, and modifications are within the scope of the following claims.

What is claimed is:

1. A method for improving success rate of glaucoma filtration surgery, comprising administering to an eye of a subject in need thereof a therapeutically effective amount of nintedanib or a pharmaceutically acceptable salt thereof.

2. The method of claim 1, wherein nintedanib is administered in the form of topical eye drop or implant.

3. The method of claim 1, wherein the amount of nintedanib administered is effective to reduce scar formation at the site of the surgery.

4. The method of claim 1, wherein the amount of nintedanib administered is effective to extend the duration of lower IOP, increase either the absolute success rate or the qualified success rate for at least 10 days, at least 90 days, at least 365 days, at least 750 days, or at least 3650 days following surgery; or wherein the amount of nintedanib administered is effective to prolong bleb survival.

5. The method of claim 1, wherein nintedanib is administered in the form of either a semi-solid or solid sustained-release implant injected into the affected eye.

6. The method of claim 1, wherein the topical ocular formulation is solution, suspension, , creams, ointments, gels, gel-forming liquid, suspension containing liposomes or micelles, spray formulation, or emulsion.

7. The method of claim 1, wherein the treatment is performed before, during or after operation.

8. The method of claim 1, wherein the glaucoma filtration surgery is performed using the classic trabeculectomy or a method selected from the group consisting of Trabectome, Gonioscopy-assisted transluminal trabeculotomy, Excimer laser trabeculostomy, and Endoscopic cyclophotocoagulation.

9. The method of claim 1, wherein the glaucoma surgery performed is for implanting an ocular filtration device.

10. The method of claim 9, wherein the ocular filtration device is an ocular stent.

11. The method of claim 9, wherein the ocular filtration device is selected from the group consisting of an iStent, Hydrus and CyPass microstent.

12. The method of claims 1, wherein nintedanib is administered in combination with a cell-proliferation-inhibiting antimetabolite drug.

13. The method of claim 12, wherein the antimetabolite drug is selected from the group consisting of Mitomycin C, 5-Fluorouracil, Floxuridine, Cytarabine, 6-Azauracil, Azathioprine, Methotrexate, Mycophenolate Mofetil, and Thiotepa.

14. A method of adjunctive treatment associated with glaucoma filtration surgery in a subject, the method comprising administering to a subject in need thereof an effective amount of a composition comprising nintedanib or a pharmaceutically acceptable salt thereof.

15. The method of claim 14, wherein composition is administered in the form of topical eye drop or implant.

16. The method of claim 14, wherein the composition contains an amount of nintedanib effective to reduce scar formation at the site of the surgery.

17. The method of claim 14, wherein the composition contains an amount of nintedanib effective to extend the duration of lower IOP, or increase either the absolute or the qualified success rate defined above, for at least 10 days, or at least 365 days, or at least 3650 days following surgery.

18. The method of claim 15, wherein the amount of nintedanib administered is effective to prolong bleb survival.

19. The method of claim 14, wherein nintedanib is administer to the eye before, during or after glaucoma filtration surgery.

20. The method of claim 14, wherein nintedanib is in either a semi-solid or solid sustained-release implant is injected into the affected eye.

21. The method of claim 14, wherein the topical ocular formulation is solution, suspension or emulsion.

22. The method of claim 14, wherein the glaucoma filtration surgery is performed using the classic trabeculectomy or a method selected from the group consisting of Trabectome, Gonioscopy-assisted transluminal trabeculotomy, Excimer laser trabeculostomy, and Endoscopic cyclophotocoagulation.

23. The method of claim 14, wherein the glaucoma surgery performed is for implanting an ocular filtration device.

24. The method of claim 23, wherein the ocular filtration device is an ocular stent.

25. The method of claim 23, wherein the ocular filtration device is selected from the group consisting of an iStent, Hydrus and CyPass microstent.

26. The method of claims1, wherein nintedanib is administered in combination with a cell-proliferation-inhibiting antimetabolite drug.

27. The method of claim 26, wherein the antimetabolite drug is selected from the group consisting of Mitomycin C, 5-Fluorouracil, Floxuridine, Cytarabine, 6-Azauracil, Azathioprine, Methotrexate, Mycophenolate Mofetil, and Thiotepa.

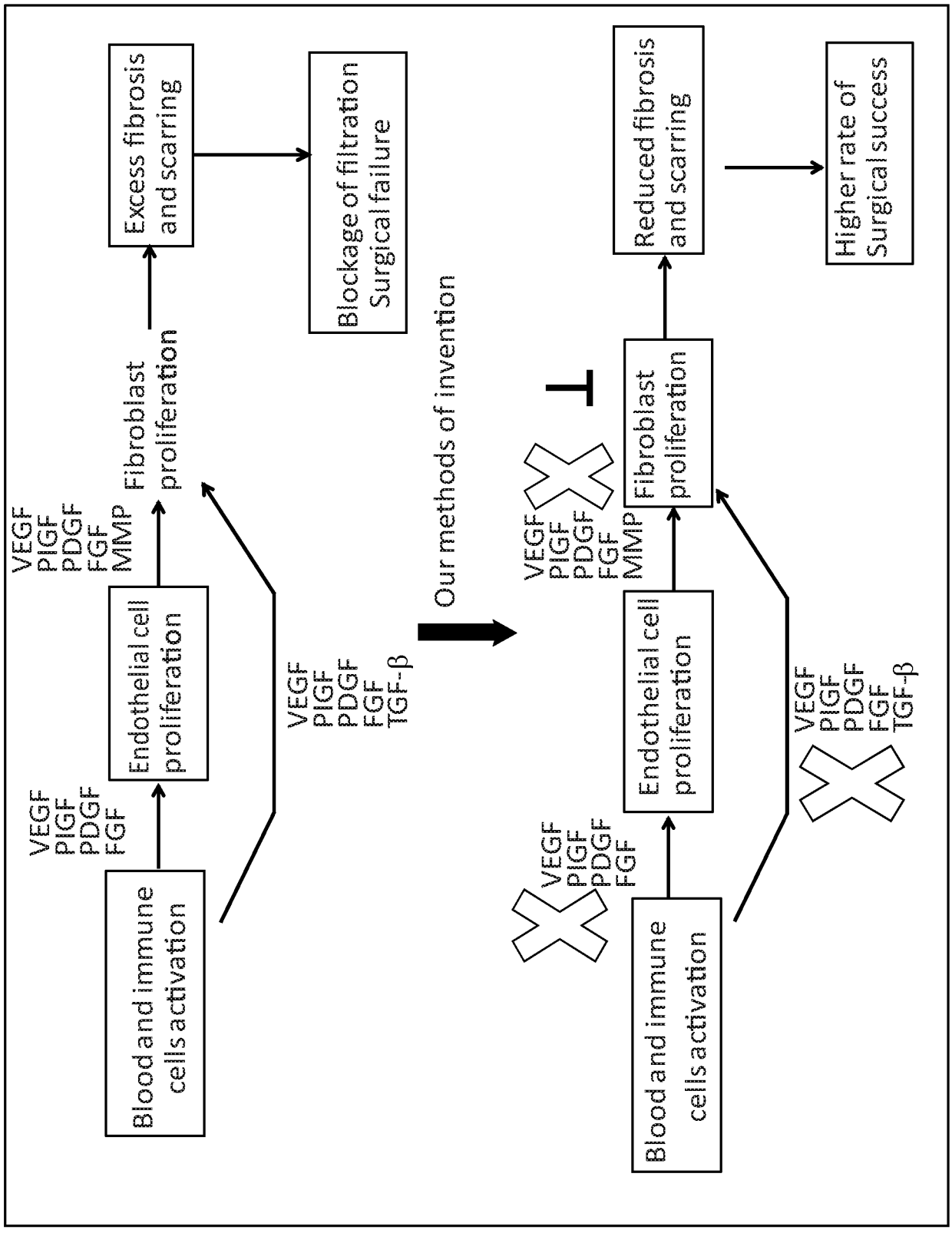
Blood and immune cells activation
VEGF PIGF PDGF FGF
Endothelial cell proliferation
VEGF PIGF PDGF FGF MMP
Fibroblast proliferation
Excess fibrosis and scarring
Blockage of filtration Surgical failure
VEGF PIGF PDGF FGF TGF-β
Our methods of invention
Blood and immune cells activation
VEGF PIGF PDGF FGF
Endothelial cell proliferation
VEGF PIGF PDGF FGF MMP
Fibroblast proliferation
Reduced fibrosis and scarring
Higher rate of Surgical success
VEGF PIGF PDGF FGF TGF-β

FIG. 1

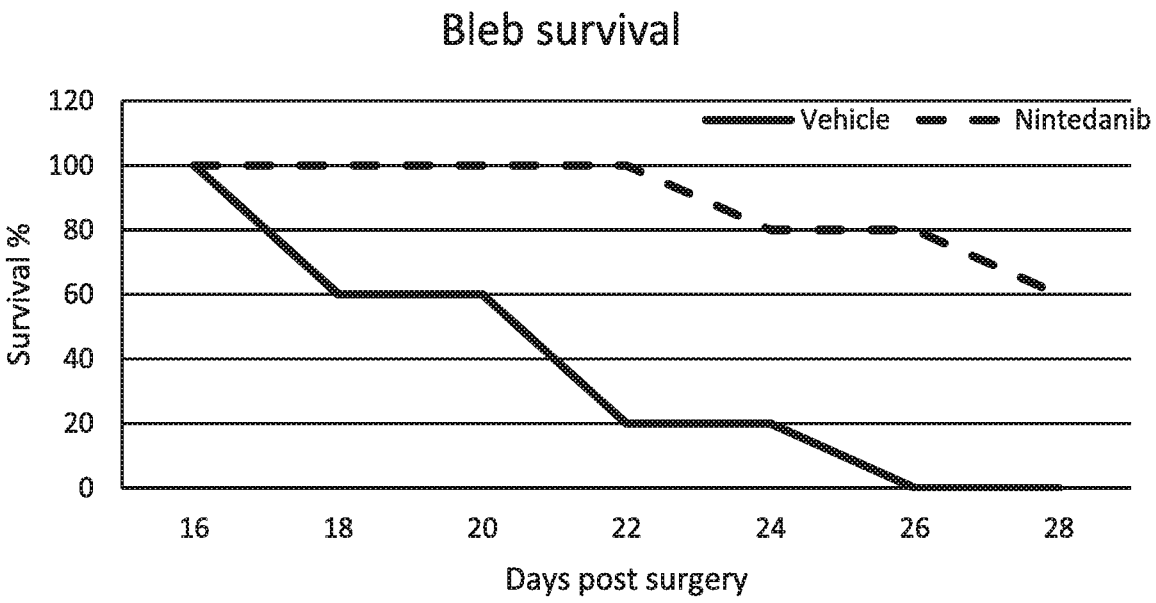
Bleb survival
Vehicle
Nintedanib
Survival %
120
100
80
60
40
20
0
16
18
20
22
24
26
28
Days post surgery

FIG. 2

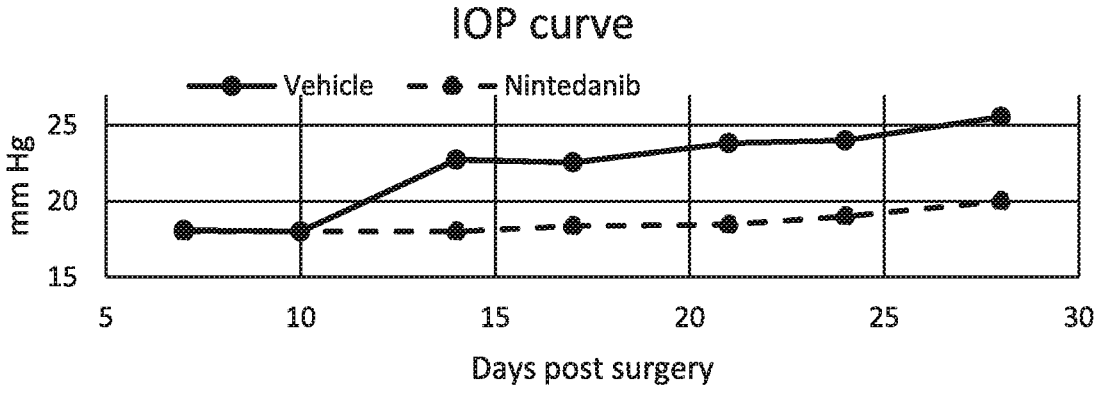
IOP curve
Vehicle
Nintedanib
mm Hg
25
20
15
5
10
15
20
25
30
Days post surgery

FIG. 3

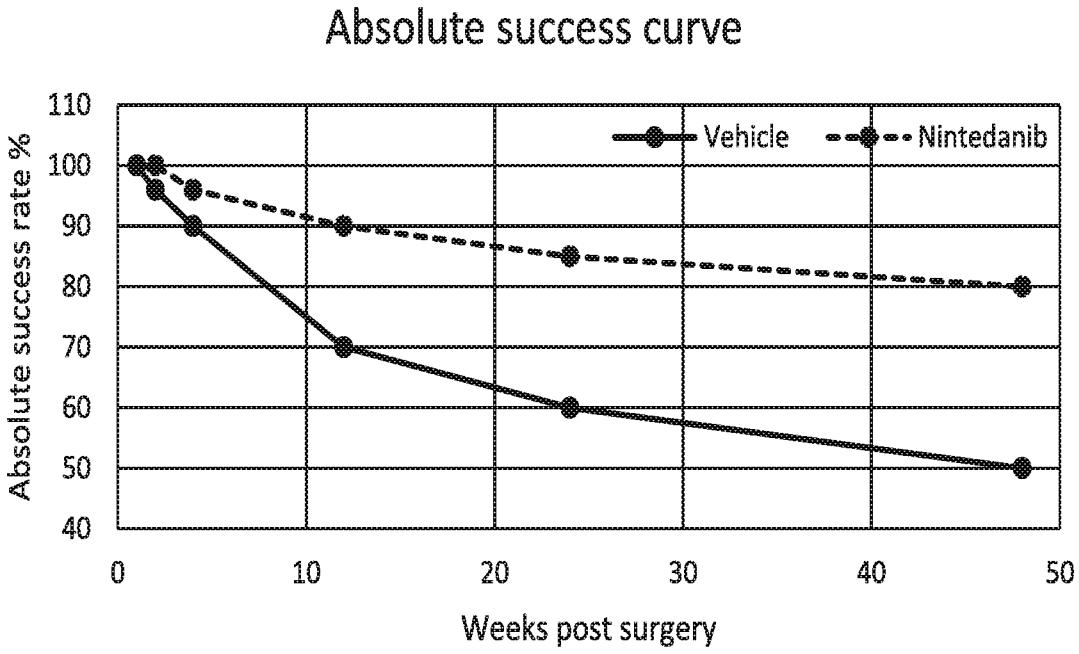
Absolute success curve
Absolute success rate %
110
100
90
80
70
60
50
40
0
10
20
30
40
50
Weeks post surgery
Vehicle
Nintedanib

FIG. 4

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US17/34792

A. CLASSIFICATION OF SUBJECT MATTER
IPC - A61F 9/00, 9/007 (2017.01)
CPC - A61F 9/00, 9/007, 9/00781

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
See Search History document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
See Search History document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X -- Y	WO 2016/029191 A2 (AUCKLAND UNISERVICES LIMITED, et al.) February 25, 2016; abstract; paragraphs [106], [168], [211], [343], [353]-[357], [395]-[397], [425], [432], [439], [458]	1-8, 14-22 ---------- 9-13, 23-27
Y	US 2015/0265469 A1 (THE REGENTS OF THE UNIVERSITY OF COLORADO, et al.) September 24, 2015; abstract; paragraph [0038]	9-11, 23-25
Y	US 2015/0258120 A1 (CLEARSIDE BIOMEDICAL, INC.) September 17, 2015; paragraphs [0011], [0165], [0180], [0190]	12-13, 26-27

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 July 2017 (26.07.2017)	25 OCT 2017
Name and mailing address of the ISA/ Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer Shane Thomas PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

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A61F 9/00(2006.01)
A61F 9/007(2006.01)

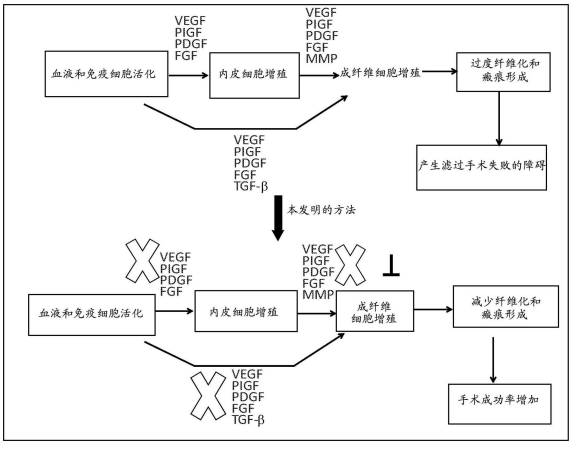
权利要求书2页 说明书13页 附图3页

(54)发明名称

使用尼达尼布改善青光眼手术成功情况的组合物和方法

(57)摘要

本申请公开了使用尼达尼布改善青光眼过滤手术成功率的组合物和方法。尼达尼布可以在局部或植入眼用制剂中单独使用或与抗代谢药物联用。



CN 109561985 A

1.一种用于改善青光眼过滤手术成功率的方法,所述方法包括向需要其的对象的眼部施用治疗有效量的尼达尼布或其药学上可接受的盐。

2.根据权利要求1所述的方法,其中尼达尼布以局部滴眼液或植入物形式施用。

3.根据权利要求1所述的方法,其中所施用的尼达尼布的量有效减少手术部位的瘢痕形成。

4.根据权利要求1所述的方法,其中所施用的尼达尼布的量在手术后有效延长较低IOP的持续时间、提高绝对成功率或合格成功率达至少10天、至少90天、至少365天、至少750天或至少3650天;或者所施用的尼达尼布的量有效延长泡体(bleb)存活。

5.根据权利要求1所述的方法,其中尼达尼布以注射至患眼的半固体或固体持续释放植入物形式施用。

6.根据权利要求1所述的方法,其中所述局部眼用制剂是溶液、混悬液、乳膏、软膏、凝胶、凝胶形成液体、含有脂质体或胶束的混悬液、喷雾制剂或乳液。

7.根据权利要求1所述的方法,其中所述治疗在手术之前,在手术期间或在手术之后进行。

8.根据权利要求1所述的方法,其中所述青光眼过滤手术使用经典的小梁切除术或选自下组的方法进行:小梁消融术(Trabectome)、前房角镜检查辅助经腔小梁切开术(Gonioscopy-assisted transluminal trabeculotomy)、准分子激光小梁造口术(Excimer laser trabeculostomy)和内窥镜睫状体光凝术(Endoscopic cyclophotocoagulation)。

9.根据权利要求1所述的方法,其中所进行的青光眼手术是为了植入眼过滤装置(ocular filtration device)。

10.根据权利要求9所述的方法,其中所述眼过滤装置是眼支架。

11.根据权利要求9所述的方法,其中所述眼过滤装置选自下组:iStent、Hydrus和CyPass微型支架。

12.根据权利要求1所述的方法,其中尼达尼布与抑制细胞增殖的抗代谢药联合施用。

13.根据权利要求12所述的方法,其中所述抗代谢药选自下组:丝裂霉素C、5-氟尿嘧啶、氟尿苷、阿糖胞苷、6-氮尿嘧啶、硫唑嘌呤、甲氨蝶呤、霉酚酸酯和硫噻吩。

14.一种与在对象中进行的青光眼过滤手术相关的辅助治疗方法,所述方法包括向需要其的对象施用治疗有效量的含有尼达尼布或其药学上可接受的盐的组合物。

15.根据权利要求14所述的方法,其中组合物以局部滴眼液或植入物形式施用。

16.根据权利要求14所述的方法,其中所述组合物含有一定量的尼达尼布以有效减少手术部位的瘢痕形成。

17.根据权利要求14所述的方法,其中所述组合物含有一定量的尼达尼布以便在手术后有效延长较低IOP的持续时间或者提高上文定义的绝对成功率或合格成功率达至少10天、至少90天、至少365天、至少750天或至少3650天。

18.根据权利要求15所述的方法,其中所施用的尼达尼布的量有效延长泡体存活。

19.根据权利要求14所述的方法,其中尼达尼布在青光眼过滤手术之前,在青光眼过滤手术期间或在青光眼过滤手术之后施用。

20.根据权利要求14所述的方法,其中尼达尼布是注射至患眼的半固体或固体持续释放植入物。

21.根据权利要求14所述的方法，其中所述局部眼用制剂是溶液、混悬液或乳液。

22.根据权利要求14所述的方法，其中所述青光眼过滤手术使用经典的小梁切除术或选自下组的方法进行：小梁消融术、前房角镜检查辅助经腔小梁切开术、准分子激光小梁造口术和内窥镜睫状体光凝术。

23.根据权利要求14所述的方法，其中所进行的青光眼手术是为了植入眼过滤装置。

24.根据权利要求23所述的方法，其中所述眼过滤装置是眼支架。

25.根据权利要求23所述的方法，其中所述眼过滤装置选自下组：iStent、Hydrus和CyPass微型支架。

26.根据权利要求1所述的方法，其中尼达尼布与抑制细胞增殖的抗代谢药联合施用。

27.根据权利要求26所述的方法，其中所述抗代谢药选自下组：丝裂霉素C、5-氟尿嘧啶、氟尿苷、阿糖胞苷、6-氮尿嘧啶、硫唑嘌呤、甲氨蝶呤、霉酚酸酯和硫噻吩。

使用尼达尼布改善青光眼手术成功情况的组合物和方法

[0001] 优先权的主张

[0002] 本申请主张2016年06月02日提出的美国临时专利申请序列号62/344,878和2016年06月02日提出的美国临时专利申请序列号62/344,870的权益,其每一个的全部内容均通过引用并入本申请。

技术领域

[0003] 本公开内容涉及包含尼达尼布的眼用组合物以及使用其改善青光眼手术成功率的方法。

背景技术

[0004] 青光眼指通常由眼压异常升高引起的一系列损伤视神经的眼部病况。降低青光眼眼压的一种方法是通过手术在眼中形成排水口。将这种手术类型称为青光眼过滤手术(例如,小梁切除术)。在青光眼手术中,将眼引流角中的一块组织切除,形成开口。这个新的开口形成一个排水口,使得液体从眼中排出。由于流体现在能够相对容易地通过新的开口排入结膜下方的储库(泡体)中,因而使得眼压降低。随后流体被机体吸收。

[0005] 作为青光眼过滤手术的结果,可能在手术部位出现瘢痕和纤维化。瘢痕和纤维化通常导致滤过逐渐减少以及失去对眼内压的控制。过度纤维化是导致瘢痕形成和青光眼过滤手术失败的关键因素。目前用于减少失败的治疗方法仍然是不足的和需要改进的。

发明内容

[0006] 在某些方面中,本公开内容提供了一种通过向需要此类治疗的对象的眼部施用尼达尼布用于改善青光眼手术(例如,青光眼过滤手术)成功率的方法。一个方面的特征在于提供了一种与在对象中进行的青光眼过滤手术相关的辅助治疗方法,所述方法包括向需要其的对象施用治疗有效量的含有尼达尼布或其药学上可接受的盐的组合物。所述方法改善了青光眼手术的成功率。青光眼手术包括例如经典的小梁切除术方法或者选自下组的方法:小梁消融术、前房角镜检查辅助经腔小梁切开术、准分子激光小梁造口术和内窥镜睫状体光凝术。所进行的青光眼手术还可以是植入眼过滤装置,其中所述眼过滤装置是眼支架。例如,眼过滤装置可以选自下组:iStent、Hydrus和CyPass微型支架。

[0007] 在本申请公开方法的一些方面中,向对象施用的尼达尼布的量在手术后至少10天、至少90天、至少365天、至少750天或至少3650天有效延长较低IOP的持续时间、提高绝对成功率或合格成功率;或者所施用的尼达尼布的量有效延长泡体存活。

[0008] 在一些方面中,尼达尼布组合物以局部眼用制剂(例如,局部滴眼液)或植入物形式施用。在一些实例中,尼达尼布是向患眼局部施用的局部眼用制剂。在某些方面中,制剂中尼达尼布的浓度以重量计或以体积计是组合物总量的0.001%至10%。在某些方面中,局部眼用制剂是溶液、混悬液或乳液。在另一个方面中,尼达尼布是注射至患眼的植入物或半固体持续释放制剂。在某些方面中,在植入物中尼达尼布的量从1μg至100mg。

[0009] 在某些方面中，所公开的方法通过将尼达尼布与抗代谢药联用实施。抗代谢药可以是但不限于丝裂霉素C、5-氟尿嘧啶、氟尿苷、阿糖胞苷、6-氮尿嘧啶、硫唑嘌呤、甲氨蝶呤、霉酚酸酯和硫噻吩。

[0010] 在另一个方面中，所公开的方法通过减少手术部位的异常血管分布和纤维化减少青光眼手术中的瘢痕形成。在某些方面中，所公开的方法在手术之前、与手术结合或在手术之后进行以减少青光眼手术的失败。因此，在一些方面中，所施用的尼达尼布的量有效减少手术部位的瘢痕形成；在一些方面中，所施用的尼达尼布的量在手术后至少10天、至少90天、至少365天、至少750天或至少3650天有效延长较低IOP的持续时间。在一些方面中，所施用的尼达尼布的量有效延长泡体存活。

[0011] 如在本申请中所使用的，术语“一个或多个”包括至少一个，更适宜地1个、2个、3个、4个、5个、10个、20个、50个、100个、500个等“一个或多个”所指的项目。

[0012] 术语“对象”指动物或人，或者来自动物或人的一种或多种细胞。优选地，对象是人。对象还可以包括非人灵长类动物。可以将人类对象称为患者。

[0013] 除非另有定义，否则本申请中所使用的所有技术和科学术语均具有与本发明所属技术领域普通技术人员的通常理解具有相同含义。本申请描述了用于本发明的方法和材料；亦可使用本领域公知的其他适宜的方法和材料。材料、方法和实施例仅是说明性的并且并非旨在进行限制。本申请提及的所有出版物、专利申请、专利、序列、数据库条目及其他参考文献的全部内容通过引用并入。在出现冲突的情况下，将以本说明书(包括定义)为准。

[0014] 本发明的其他特征及优点从下述详细说明和附图以及从权利要求中将显而易见。

附图说明

[0015] 图1是显示减少过量瘢痕形成和改善青光眼手术成功率的示例性机制的流程图。

[0016] 图2是显示在家兔模型中青光眼过滤手术后泡体存活的图。

[0017] 图3是显示在家兔模型中青光眼过滤手术后眼压(IOP)的图。

[0018] 图4是显示根据本申请公开的方法在临床研究中青光眼过滤手术绝对成功率的图。

具体实施方式

[0019] 青光眼是一系列以视网膜神经节细胞(“RGC”)死亡、特定视野丧失和视神经萎缩为特征的疾病。青光眼是在世界范围内导致失明的原因。有效降低眼压(“IOP”)的各种治疗选择可用于控制以及可能延缓疾病进展。治疗选择包括例如药物治疗(即，IOP降低药)、激光眼科手术和/或常规手术方法，如青光眼过滤手术(或者也称为过滤手术或小梁切除术)。

[0020] 尽管在发达国家广泛使用局部IOP降低药，但是青光眼手术仍在世界其他地区广泛使用(特别是针对闭角型青光眼)。青光眼手术具有随着时间的推移成本较低的优点，并且不存在与需要每日多次应用局部滴眼液相关的依从性问题。传统青光眼过滤手术和小梁切除术具有较高失败率(Schlunck等，Exp Eye Res.2016;142:76-82)以及植入眼过滤装置(例如，青光眼过滤装置)的方法也存在长期失效的问题(Amoozgar等，Curr Opin Ophthalmol.2016;27(2):164-9)。失败的原因是术后伤口过度愈合，随后出现阻碍引流的纤维化的瘢痕形成。手术对组织的损伤通常会诱导促炎性核促纤维化因子，其导致异常细

胞外基质改变和纤维化。由这些因子诱导的肌成纤维细胞过度增殖随后引起过度的纤维化和瘢痕形成。

[0021] 已在青光眼手术过程中或手术后施用抗代谢药丝裂霉素C(MMC)作为抗瘢痕剂。在随访过程中还使用主要通过局部注射的另一种抗代谢药5-氟尿嘧啶(5-FU)(Schlunck等,Exp Eye Res.2016;142:76-82)。这些抗代谢药通过阻断成纤维细胞的快速增殖发挥作用。其活性不是选择性的且已知会引起副作用。例如,抗细胞分裂活性有时会导致术后的泡体渗漏。更好的青光眼术后管理仍是一个尚未满足的医疗需求。

[0022] 由于导致青光眼手术后瘢痕形成的因素很多,单独靶向任何单一通路可能不足以改善手术的成功情况。本公开内容通过向眼部施用具有下述关键属性的组合物改善青光眼手术的成功情况:1)组合物将同时抑制下文公开的若干重要的病理途径;2)组合物利用小分子药物而不是抗体药物实现向靶组织更有效的药物递送;3)组合物是滴眼液或植入物形式的局部制剂,以便向手术部位方便地和一致地进行药物递送;以及4)组合物含有尼达尼布,可以将其与抗代谢药联用以实现在改善青光眼过滤手术的成功情况方面的相加或协同作用。

[0023] 本公开内容提供了一种在手术之前、手术过程中或手术之后使用含有尼达尼布的局部制剂(例如,局部滴眼液、植入物)的方法。尼达尼布满足抑制血管内皮生长因子(“VEGF”)受体(“VEGFR”)1-3、血小板衍生生长因子受体(PDGFR)-α和-β以及成纤维细胞生长因子受体2(“FGFR2”)以达到所需疗效的要求。

[0024] 不受理论的束缚,应当理解的是抑制VEGFR的所有成员是重要的,因为除了VEGF以外还需要阻断胎盘生长因子(“PIGF”)。PIGF仅作用于病理性血管生成和炎症并且更多是与青光眼手术相关的问题相关(Van Bergen等,J Cell Mol Med.2013;17(12):1632-43)。对于青光眼过滤手术而言,所公开的方法还抑制FGFR2,因为其在瘢痕形成中具有作用。本申请公开的局部制剂能够便于在手术之前、手术过程中和手术之后进行治疗。本申请公开的改善青光眼手术成功率的机制如图1中所示,其显示了在适宜眼用制剂中的尼达尼布将同时阻断参与伤口过度愈合的关键病理性因子(包括PIGF、VEGF、PDGF,FGF)的信号通路,以及将通过减少瘢痕形成增加青光眼手术的成功。

[0025] 如在本申请中所使用的,术语“改善青光眼手术的成功情况”指在手术后至少10天、至少90天、至少365天、至少750天或至少3650天的一段时间内延长降低的(即,较低)IOP的持续时间,在手术后给定的一段时间内(例如,至少10天、至少90天、至少365天、至少750天或至少3650天)与手术前的基线相比IOP降低百分比增加,在给定的一段时间内绝对(也称为完全)成功率(定义为保持在正常IOP范围内且与未给予任何青光眼药物的基线相比具有降低的IOP的患者百分比)增加,在一段时间内(例如,至少10天、至少90天、至少365天、至少750天或至少3650天)合格的成功率增加(定义为保持在正常IOP范围内且与给予青光眼药物的基线相比具有降低的IOP的患者百分比),在一段时间内(例如,至少10天、至少90天、至少365天、至少750天或至少3650天)泡体的分级和存活情况改善。

[0026] 如在本申请中所使用的,“正常IOP”或“正常IOP范围”指在人眼中的眼压在约5mm Hg至约22mmHg之间,或者约10mm Hg至约21mmHg之间。

[0027] 在本申请中使用的术语“治疗(treatment、treating、treat)”等通常指获得所需的药理学和/或生理学效应。该效应就完全或部分防止疾病或其症状而言可以是预防性的

和/或就部分或完全稳定或治愈疾病和/或归因于该疾病的不良反应而言可以是治疗性的。术语“治疗”包含对在哺乳动物(特别是人类)中的疾病的任何治疗,并且包括:(a)在可能易患疾病或症状但尚未诊断为患有该疾病或症状的对象中防止疾病和/或症状的出现;(b)抑制疾病和/或症状,即阻止其发展;或(c)减轻疾病症状,即引起疾病和/或症状消退。需要治疗的那些包括已患病的那些(例如,患有高IOP的那些、患有感染的那些等等)以及希望预防的那些(例如,青光眼易感性增加的那些、怀疑具有高IOP的那些等等)。

[0028] 尼达尼布{(3Z)-3-{[(4-{甲基[(4-甲基六氢吡嗪-1-基)乙酰基]氨基}苯基)氨基](苯基)亚甲基}-2-氧代-2,3-二氢-1H-吲哚-6-羧酸甲酯}是一种如本申请所述的激酶抑制剂。尼达尼布主要抑制受体酪氨酸激酶,包括例如血管内皮生长因子受体(VEGFR1-3)、血小板衍生的生长因子受体(PDGFRα和β)、成纤维细胞生长因子受体(FGFR 1-4)。

[0029] 制剂和给药方案

[0030] 本申请所述的方法包括药物组合物的生产和使用,其包括通过本申请所述的方法鉴定作为活性成分的化合物。还包括药物组合物本身。

[0031] 药物组合物通常包含药学上可接受的赋形剂。如在本申请中所使用的,用语“药学上可接受的赋形剂”或“药学上可接受的载体”包括与药物施用相容的盐水、溶剂、分散介质、包衣、抗细菌和抗真菌剂、等渗剂和吸收延迟剂等。

[0032] 如在本申请中所使用的短语“药学上可接受的盐”指向哺乳动物施用是安全和有效的且具有所需的生物活性的目标化合物的盐。药学上可接受的酸式盐包括但不限于盐酸盐、氢溴酸盐、氢碘酸盐、硝酸盐、硫酸盐、硫酸氢盐、磷酸盐、酸式磷酸盐、异烟酸盐、碳酸盐、碳酸氢盐、乙酸盐,乳酸盐、水杨酸盐、柠檬酸盐、酒石酸盐、丙酸盐、丁酸盐、丙酮酸盐、草酸盐、丙二酸盐、泛酸盐、酒石酸氢盐、抗坏血酸盐、琥珀酸盐、马来酸盐、龙胆酸盐、富马酸盐、葡糖酸盐、葡糖醛酸盐、糖酸盐、甲酸盐、苯甲酸盐、谷氨酸盐、甲磺酸盐、乙磺酸盐、苯磺酸盐、对甲苯磺酸盐和双羟萘酸(即,1,1’亚甲基-双-(2-羟基-3-萘甲酸))盐。适宜的碱式盐包括但不限于铝、钙、锂、镁、钾、钠、锌、铋和二乙醇胺盐。

[0033] 用于将适宜的药物组合物制剂的方法是本领域公知的,参见例如Remington:The Science and Practice of Pharmacy,第21版,2005;以及Drugs and the Pharmaceutical Sciences:a Series of Textbooks and Monographs(Dekker,NY)系列书籍。例如,用于眼科应用的溶液、混悬液或乳液可以包含下述组分:无菌稀释剂,如注射用水、盐水溶液、不挥发油、聚乙二醇、甘油、丙二醇或其他合成溶剂;抗细菌剂;抗氧化剂;螯合剂;缓冲剂,如乙酸盐、柠檬酸盐或磷酸盐以及张力调节剂,如氯化钠或右旋糖。可以使用酸或碱(如盐酸或氢氧化钠)调节pH。

[0034] 适于注射使用的药物组合物可以包含无菌水溶液(若可溶于水)或分散液以及用于即时制备无菌可注射溶液或分散液的无菌粉末。其在生产和储存的条件下应该是稳定的,并且必须防止诸如细菌和真菌等微生物的污染作用。载体可以是溶剂或分散介质,其含有例如水、乙醇、多元醇(例如,甘油、丙二醇和液体聚乙二醇等)及其适宜的混合物。可以例如通过使用包衣(如卵磷脂)、通过在分散液情况下维持所需粒径以及通过使用表面活性剂来维持适当的流动性。可以通过使用各种抗细菌和抗真菌剂防止微生物的作用,例如对羟基苯甲酸酯、氯丁醇、苯酚、抗坏血酸、硫柳汞等。在很多情况下,在组合物中包含等渗剂,例如糖、多元醇(如甘露醇、山梨醇)以及氯化钠将是优选的。可以通过在组合物中包含延迟吸

收的试剂(例如单硬脂酸铝和明胶)来实现可注射组合物的延长吸收。

[0035] 可以通过下述步骤制备无菌可注射溶液:将所需量的活性化合物掺入具有一种上文所列成分或这些成分的组合(根据需要)的适当溶剂中,随后过滤除菌。在通常情况下,通过将活性化合物掺入无菌载剂中制备分散液,该无菌载剂含有基本分散介质和来自上文所列出那些的所需的其他成分。在用于制备无菌可注射溶液的无菌粉末的情况下,优选的制备方法是真空干燥和冷冻干燥,其由其此前的无菌过滤溶液生产活性成分加上任意其他所需成分的粉末。

[0036] 在一个实施方式中,使用将保护治疗化合物抵抗体内快速消除的载体制备治疗化合物,如控释制剂,包括植入物和微囊化递送系统。可以使用生物可降解的生物相容性聚合物,如乙烯基乙酸乙烯酯、聚酸酐、聚乙醇酸、胶原、聚原酸酯和聚乳酸。可以使用标准技术制备或以商业方式获得此类制剂。

[0037] 可以将药物组合物连同施用说明书一起置于容器、包装或分配器中。

[0038] 可以局部(例如,以局部眼用制剂形式)施用或以半固体制剂或固体植入物的注射剂形式施用,或者通过本领域公知的任意其他适宜方法施用尼达尼布的组合物和制剂。尽管可以原样使用本申请所公开的药剂,但是优选的是以药物制剂的形式施用药剂,例如与根据预期给药途径和标准药物实践选择的合适的药物赋形剂、稀释剂或载体混合。药物制剂包含至少一种与药学上可接受的赋形剂、稀释剂和/或载体联合的活性化合物。

[0039] 本申请公开的药物组合物可以包含“治疗有效量”的本申请所述的药剂。可以根据所施用药剂的作用,或者如果使用一种以上药剂,则根据药剂的组合作用,确定这种有效量。药剂的治疗有效量也可以根据诸如个体的疾病状态、年龄、性别和体重,以及化合物在个体中激发所述应答的能力(例如,至少一种病症参数改善或病症的至少一种症状改善)的因素而改变。治疗有效量也是其中治疗有益效果超过组合物的任何毒性或有害作用的量。

[0040] 用于治疗病症的本公开组合物的有效剂量可以根据多种不同因素而改变,包括施用方法、靶点位置、对象的生理状态、对象是人还是动物、所施用的其他药物以及治疗是预防性的还是治疗性的。可以使用本领域技术人员公知的常规方法滴定治疗剂量以优化安全性和有效性。

[0041] 在一些例子中,局部眼用制剂是溶液、混悬液、乳膏、软膏、凝胶、凝胶形成液体、含有脂质体或胶束的混悬液、喷雾制剂或乳液。在一些例子中,局部眼用制剂还包含一种或多种选自下组的药学上可接受的赋形剂:稳定剂、表面活性剂、基于聚合物的载体、胶凝剂、有机助溶剂、pH活性成分、渗透活性成分以及含有或不含防腐剂。在一些例子中,将持续释放半固体制剂、持续释放固体制剂或眼用植入物注射至患眼。在一些实施方式中,持续释放半固体制剂、持续释放固体制剂或眼用植入物还包含药学上可接受的赋形剂。在一些例子中,持续释放半固体制剂、持续释放固体制剂或眼用植入物包括多激酶抑制剂、抗代谢物或其组合;以及选自下组的可生物降解的聚合物:聚乳酸(PLA)、聚乙醇酸(PLGA)和聚乳酸聚乙醇酸共聚物。

[0042] 组合物或制剂的施用可以是每天一次、每天两次、每天三次、每天四次或更高频率。在治疗的治疗维持期可以降低频率,例如以每两天或三天一次代替每天一次或每天两次。可以根据治疗医师的判断调整剂量和施用频率,例如考虑使用本发明方法所治疗病况的疾病的临床指征、病理学指征以及临床和亚临床症状,以及患者的临床病史。

[0043] 应当认识到的是，用于治疗中所需的本申请所公开的药剂的量将随施用途径、所需治疗的病况的性质以及患者的年龄、体重和病况而改变且最终将由主治医师来决定。组合物通常将含有有效量的尼达尼布。可以根据动物实验确定初始剂量，且可以根据本领域公认的实践来进行用于人类给药的剂量的缩放。

[0044] 治疗长度(即，天数)将由治疗对象的医师容易地确定；然而，治疗天数可在约1天至约365天范围内变化。如本发明方法所提供的，可以在治疗期间对疗效进行监测以确定治疗是否成功，或者是否需要额外的(或修改)治疗。

[0045] 治疗化合物的剂量、毒性和疗效可以在细胞培养物或实验动物中通过标准药物程序确定，例如用于确定LD50(对群体的50％致死的剂量)和ED50(在群体的50％中治疗有效的剂量)的程序。尼达尼布的剂型可以由本领域普通技术人员容易地确定，且可以例如在根据本领域公知的标准方法确定剂量、安全性和有效性的动物模型中和在文献中报道的临床研究中获得。确切的制剂、施用途径和剂量可以由个别医师根据患者的病况来选择

[0046] 用于本发明方法中的组合物可以包含以组合物总量的重量或体积计0.001％至10％浓度的尼达尼布。例如，水性组合物包含0.001％、0.01％、0.1％、0.5％、1.0％、1.5％、2.0％、5.0％或至多10％的尼达尼布。

[0047] 如本领域技术人员所熟悉的，向眼部施用的水溶液可以是粒子滴管或吸管或其他专用无菌装置的“滴”或数滴(例如，尼达尼布溶液)的形式。此类滴通常将是以体积计至多50微升，但可能更少，例如少于10微升。

[0048] 实施例

[0049] 在下述实施例中进一步描述了本发明，这些实施例并不限制在权利要求书中所描述的本发明的范围。

[0050] 实施例1:家兔青光眼手术模型

[0051] 采用家兔青光眼手术模型用于说明使用本发明公开的方法来改善青光眼过滤手术的成功情况。特别地，将已建立的家兔青光眼过滤手术模型用于研究0.2％尼达尼布溶液对手术后伤口愈合事件的影响。手术程序如Wong等所述(Wong等，Invest Ophthalmol Vis Sci.2003;44(3):1097-1103)。简言之，将部分撕裂8-0丝质角膜牵引缝合线置于上方，并将眼部拉下。将基于穹窿的结膜瓣抬起，之后沿着角膜缘约5mm进行结膜下空间的钝性解剖，并且向后8mm。使用微型视网膜(MVR)刀在角膜缘后3至4mm处形成部分撕裂的巩膜切口，并形成到角膜基质的巩膜隧道。使22号、25-mm静脉内插管(Venflon 2;Beckton Dickinson,Oxford,UK)向前穿过巩膜隧道，直至在透明角膜中可见套管针。使套管针进入前房，然后在套管前进到瞳孔中段时撤回。修剪套管并使其在巩膜末端倾斜，以使其从插入点突出1mm，并放置10-0尼龙缝合线以将管固定到巩膜表面。使用两条间断的缝合线以及一条中央褥式10-0尼龙缝合线关闭结膜切口，该缝合线连接在针头(B/V 100-4;Ethicon)上，以形成水密性封闭。手术结束时，分别向眼中滴入一滴氯霉素和Betnesol-N(Glaxo Wellcome,Uxbridge,UK)软膏。

[0052] 实验开始前，使20只雌性新西兰白兔(2-2.4kg，12-14周龄;Charles River)适应5天。如上所述的青光眼手术在左眼进行。手术后，将家兔分成两组，一组使用载剂治疗，另一组使用0.2％尼达尼布溶液治疗。手术后立即开始治疗，治疗为每日3次共持续2周。将对手术后形成的泡体的存活情况以及眼压(IOP)随访28天。将在研究结束时进行瘢痕组织的组

织学分析。

[0053] 结果

[0054] 与载剂组相比，尼达尼布组将显著延长手术成功结局。图2提供了显示手术后泡体存活曲线的图。如图2中所示，与载剂组相比，尼达尼布组显示出显著延长的泡体存活。在第28天研究结束时，载剂组中没有泡体存活，而在尼达尼布组中大多数泡体均存活。图3a是显示手术后随访期间IOP曲线的图。在尼达尼布组中的IOP仍较低(即，低于20mm Hg)，而在载剂组中的IOP逐渐升高。差异在统计上是显着的。除了泡体存活和IOP变化以外，对手术部位瘢痕组织的组织学分析显示，尼达尼布组与载剂组相比具有更少的瘢痕组织。

[0055] 本实验的结果表明0.2％尼达尼布溶液增加青光眼手术的成功情况(即，在手术后延长泡体存活、延长较低IOP的持续时间和/或减少纤维化/瘢痕形成)。

[0056] 实施例2：将尼达尼布局部眼用制剂作为青光眼过滤手术的辅助疗法

[0057] 在一项临床研究中，将局部给予0.2％尼达尼布作为辅助疗法以增加小梁切除术的成功情况。在一项随机、双盲、安慰剂对照、为期12个月的试验中考察了局部给予0.2％尼达尼布对小梁切除术成功率的影响。研究设计如Vandewalle等所述(Vandewalle等，Br J Ophthalmol.2014,Jan;98(1):73-8)。

[0058] 将入组按计划进行原发性小梁切除术的药物无法控制的开角型青光眼患者并使其随机接受每日三次每次一滴尼达尼布或安慰剂溶液的治疗。在手术后立即开始治疗，治疗将持续1个月。在本研究中入组了约150名患者。

[0059] 手术将由有经验的外科医师采用经改良的Moorfields技术在全身或球后麻醉下进行。使用Goldmann压平眼压计测量IOP。由盲态观察者进行两次测量，如果两次结果之间的差异在2mm Hg内，则将其取平均值以确定平均IOP。如果前两个结果之前的差异>2mm Hg，则进行第三次测量。

[0060] 在小梁切除术后第1天；第1、2和4周；以及第3、6和12个月对患者进行检查。将对所有患者进行全面的眼科检查，包括测量最佳矫正视力、包括Seidel测试在内的裂隙灯检查、测量IOP以及使用90屈光度镜片的眼底生物显微镜检查。还将记录术后使用降眼压药物的数量、书中和术后并发症以及手术干预情况。

[0061] 将绝对成功情况作为主要终点，将其定义为眼压(IOP)≤21mm Hg且>5mm Hg，眼压与基线相比降低至少20％且无光感损失。

[0062] 结果

[0063] 与基线相比，在12个月访视时，尼达尼布和安慰剂组的IOP均有效降低。如图4中所示，尼达尼布组青光眼手术的绝对成功率(即，手术后超过12个月保持IOP低于约20mm Hg)高于安慰剂组。在6个月时间点时，差异具有统计学显著性。

[0064] 实施例3：制剂

[0065] 尼达尼布眼用溶液

[0066] 药品是在2-羟丙基β环糊精或其他类似环糊精以及缓冲溶液(pH范围从5.5至8.0)中制备的等渗眼用溶液。可以添加其他增粘剂、润滑剂、防腐剂以增强制剂的功能。眼用溶液的组成参见表1。

[0067] 表1尼达尼布眼用溶液

[0068]

成分	功能	浓度范围（%w/v）
CBT-001（尼达尼布游离碱）	活性药物成分	0.001 – 10
羧甲基纤维素钠（Sodium carboxymethylcellulose）	增粘剂/缓解干眼	0 – 1
Pemulen TR	增粘剂	0 – 0.2
聚乙烯醇	增粘剂/润滑剂	0 – 1.5
羟丙甲纤维素	润滑剂/缓解干眼	0 - 1
卡波姆	润滑剂/缓解干眼	0 – 0.5
羧甲基纤维素钠（Carmellose sodium）	润滑剂/缓解干眼	0 – 1
透明质酸钠	润滑剂/缓解干眼	0 – 1.5
聚乙二醇 400	润滑剂/缓解干眼	0 – 0.4
丙二醇	润滑剂/缓解干眼	0 – 0.6
2-羟丙基 β 环糊精	增溶剂	0 - 10
磺丁基-β-环糊精	增溶剂	0 - 10
随机甲基化的 β-环糊精	增溶剂	0 – 5
α-环糊精	增溶剂	0 - 4
β-环糊精	增溶剂	0 - 1
γ-环糊精	增溶剂	0 - 1
泊洛沙姆 188 或 237 或 407	增溶剂/润滑剂	0 – 5
聚山梨醇酯 80	增溶剂/润滑剂/表面活性剂	0 – 1
乙二胺四乙酸钠	螯合剂/防腐剂	0 – 0.01
苯扎氯铵	防腐剂	0 – 0.02

[0069]

成分	功能	浓度范围（%w/v）
单水合磷酸二氢钠	缓冲剂	0 – 0.43
七水合磷酸氢二钠	缓冲剂	0 – 0.8
硼酸	缓冲剂	0 – 0.6
十水合硼酸钠	缓冲剂	0 – 0.045
单水合柠檬酸	缓冲剂/防腐剂	0 – 0.13
二水合柠檬酸钠	缓冲剂/防腐剂	0 – 0.45
甘油	等渗剂	0 – 2.2
氯化钠	等渗剂	0 – 0.83
1N 氢氧化钠	pH 调节	pH 5.5 – 8.0
1N 盐酸		
注射用水	载剂	补足至 100

[0070] 尼达尼布眼用混悬液

[0071] 药品是在羧甲基纤维素钠以及缓冲溶液(pH范围从5.5至8.0)中制备的等渗眼用混悬液。药物粒径减少至小于40微米。可以添加其他增粘剂、润滑剂、增溶剂和防腐剂以增强制剂混悬液的功能。组成如表2中所示。

[0072] 表2尼达尼布眼用混悬液

[0073]

成分	功能	浓度范围（%w/v）
CBT-001（尼达尼布游离碱）	活性药物成分	0.001 – 10
羧甲基纤维素钠（Sodium carboxymethylcellulose）	增粘剂/缓解干眼	0 – 1
Pemulen TR	增粘剂	0 – 0.2

[0074]

成分	功能	浓度范围（%w/v）
聚乙烯醇	增粘剂/润滑剂	0 – 1.5
羟丙甲纤维素	润滑剂/缓解干眼	0 - 1
卡波姆	润滑剂/缓解干眼	0 – 0.5
羧甲基纤维素钠（Carmellose sodium）	润滑剂/缓解干眼	0 – 1
透明质酸钠	润滑剂/缓解干眼	0 – 1.5
聚乙二醇 400	润滑剂/缓解干眼	0 – 0.4
丙二醇	润滑剂/缓解干眼	0 – 0.6
2-羟丙基 β 环糊精	增溶剂	0 - 10
磺丁基-β-环糊精	增溶剂	0 - 10
随机甲基化的 β-环糊精	增溶剂	0 – 5
α-环糊精	增溶剂	0 - 4
β-环糊精	增溶剂	0 - 1
γ-环糊精	增溶剂	0 - 1
泊洛沙姆 188 或 237 或 407	增溶剂/润滑剂	0 – 5
聚山梨醇酯 80	增溶剂/润滑剂/表面活性剂	0 – 1
乙二胺四乙酸钠	螯合剂/防腐剂	0 – 0.01
苯扎氯铵	防腐剂	0 – 0.02
单水合磷酸二氢钠	缓冲剂	0 – 0.43
七水合磷酸氢二钠	缓冲剂	0 – 0.8
硼酸	缓冲剂	0 – 0.6
十水合硼酸钠	缓冲剂	0 – 0.045
单水合柠檬酸	缓冲剂/防腐剂	0 – 0.13
二水合柠檬酸钠	缓冲剂/防腐剂	0 – 0.45
甘油	等渗剂	0 – 2.2
氯化钠	等渗剂	0 – 0.83
1N 氢氧化钠	pH 调节	pH 5.5 – 8.0
1N 盐酸		
注射用水	载剂	补足至 100

[0075] 尼达尼布眼用乳剂

[0076] 药品是等渗眼用乳液。将药物溶解在油相和乳化剂赋形剂的混合物中，然后将其

乳化并与水相(pH范围从5.5至8.0)混合。可以添加其他增粘剂、润滑剂、增溶剂和防腐剂以增强乳液制剂的功能。组成如表3中所示。

[0077] 表3 尼达尼布眼用乳剂

[0078]

成分	功能	浓度（% w/w）
CBT-001（尼达尼布游离碱）	活性药物成分	0.001 - 10
蓖麻油	油溶剂	0 – 1.25
聚烃氧-40-硬脂酸酯	乳化剂	0 – 0.25
聚山梨醇酯 80	增溶剂/乳化剂/表面活性剂	0 - 1
磺丁基-β-环糊精	增溶剂	0 - 5
2-羟丙基-β-环糊精	增溶剂	0 - 5
随机甲基化的 β-环糊精	增溶剂	0 – 5
α-环糊精	增溶剂	0 - 4
β-环糊精	增溶剂	0 - 1
γ-环糊精	增溶剂	0 - 1
甘油	等渗剂	0 - 2.2
氯化钠	等渗剂	0 – 0.83
Pemulen TR2	增粘剂	0 – 0.1
羧甲基纤维素钠（Sodium carboxymethylcellulose）	增粘剂	0 – 0.5
聚乙烯醇	增粘剂/润滑剂	0 – 1.5
羟丙甲纤维素	润滑剂/缓解干眼	0 - 1
卡波姆	润滑剂/缓解干眼	0 – 0.5
羧甲基纤维素钠（Carmellose sodium）	润滑剂/缓解干眼	0 – 1
透明质酸钠	润滑剂/缓解干眼	0 – 1.5
聚乙二醇 400	润滑剂/缓解干眼	0 – 0.4
丙二醇	润滑剂/缓解干眼	0 – 0.6
泊洛沙姆 188 或 237 或 407	增溶剂/润滑剂	0 – 5
硼酸	缓冲剂	0 – 0.6
十水合硼酸钠	缓冲剂	0 – 0.045
单水合柠檬酸	缓冲剂/防腐剂	0 – 0.13
二水合柠檬酸钠	缓冲剂/防腐剂	0 – 0.45
单水合磷酸二氢钠	缓冲剂	0 – 0.43
七水合磷酸氢二钠	缓冲剂	0 – 0.8

[0079]

成分	功能	浓度（% w/w）
1N & 5N 氢氧化钠	pH 调节	pH 5.5 – 8.0
1N 盐酸		
注射用水	水性载剂	补足至 100

[0080] 尼达尼布持续释放半固体制剂

[0081] 药品是等渗持续释放半固体制剂。将药物溶解和/或混悬在半固体介质(pH范围从5.5至8.0)中。可以添加其他增粘剂、润滑剂、增溶剂和防腐剂以增强持续释放半固体制剂的功能。组成如表4中所示。

[0082] 表4持续释放半固体制剂

[0083]

成分	功能	浓度（% w/w）
CBT-001（尼达尼布游离碱）	活性药物成分	0.001 - 10
黄原胶	增粘剂/增稠剂	0 - 10
羟丙基甲基纤维素	增粘剂/增稠剂	0 – 10
透明质酸钠	增粘剂/增稠剂	0 – 5
透明质酸	增粘剂/增稠剂	0 - 5
硼酸	缓冲剂	0 – 0.6
十水合硼酸钠	缓冲剂	0 – 0.045
单水合柠檬酸	缓冲剂/防腐剂	0 – 0.13
二水合柠檬酸钠	缓冲剂/防腐剂	0 – 0.45
单水合磷酸二氢钠	缓冲剂	0 – 0.43
七水合磷酸氢二钠	缓冲剂	0 – 0.8
1N 和 5N 氢氧化钠	pH 调节	pH 5.5 – 8.0
1N 盐酸		
注射用水	水性载剂	补足至 100

[0084] 尼达尼布持续释放植入物

[0085] 药品是固体植入物。将药物与一种或多种聚合物混合和掺和。将药物与聚合物的混合物在预定温度下融化并挤出成具有预定直径尺寸的丝。将制剂丝切割成可以植入眼部组织中的预定尺寸的段。组成如表5中所示。

[0086] 表5持续释放植入物

[0087]

成分	功能	浓度（% w/w）
CBT-001（尼达尼布游离碱）	活性药物成分	0.001 - 10
聚(D,L-乳酸交酯)，i.v. 0.25-0.35 dL/g	聚合物	0 – 100
聚(D,L-乳酸交酯-共-乙交酯)，i.v. 0.14-0.22 dL/g	聚合物	0 – 100
聚(D,L-乳酸交酯)，i.v. 0.16-0.25 dL/g	聚合物	0 - 100
聚乙二醇 3350	聚合物	0 – 20
Resomer®RG755S	聚合物	0 - 100
Resomer®RG753H	聚合物	0 - 100

[0088] 不受限制地，用于根据本发明方法的示例性组合物可以从现有眼科可接受的组合物进行修改。

[0089] 其他实施方式

[0090] 应当理解的是，虽然已经结合其详细说明阐述了本发明，但是前述说明旨在是解释性的而非限制本发明的范围，本发明的范围由所附权利要求的范围限定。其他方面、优点和修改在下述权利要求的范围内。

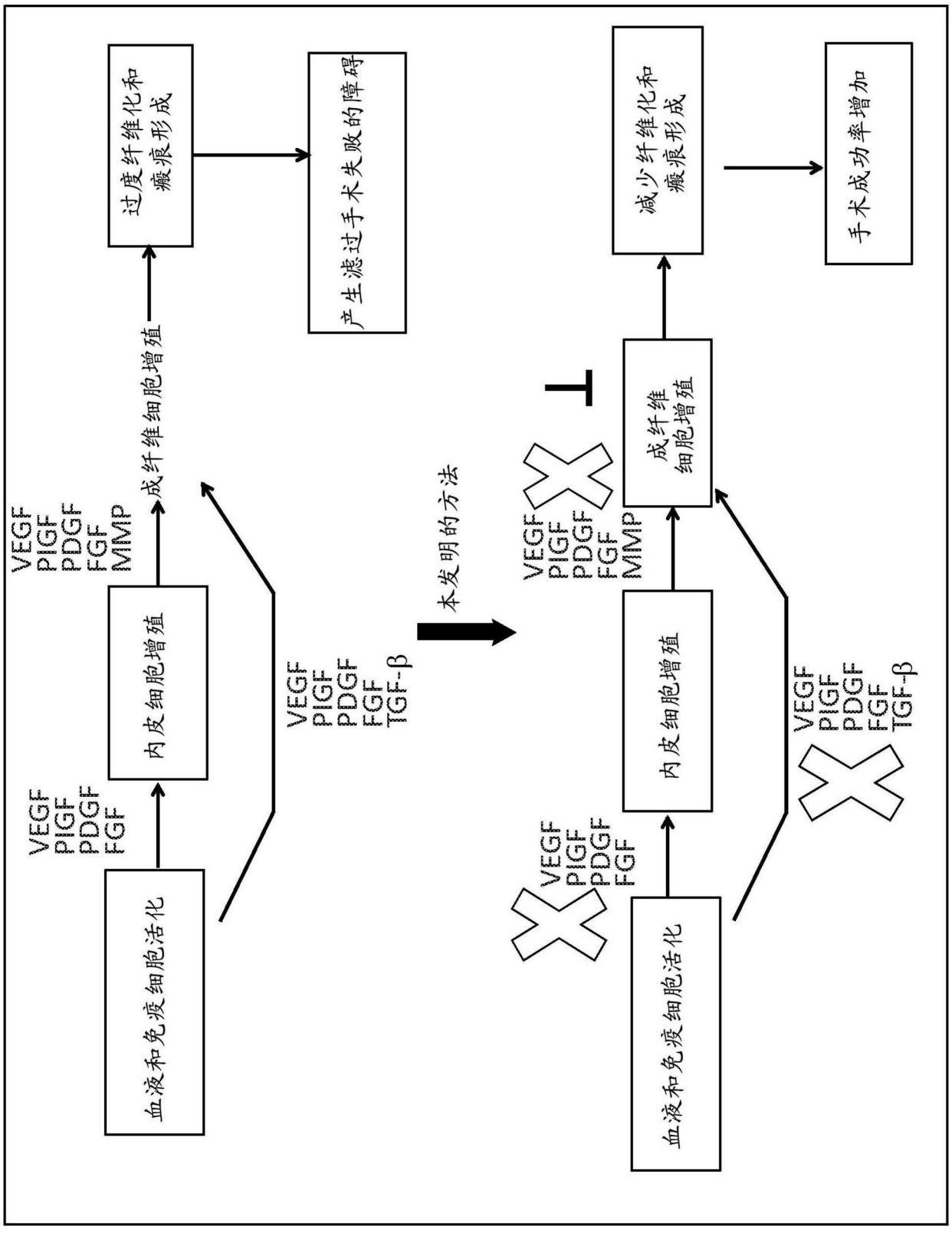

血液和免疫细胞活化
VEGF
PIGF
PDGF
FGF
内皮细胞增殖
VEGF
PIGF
PDGF
FGF
MMP
成纤维细胞增殖
过度纤维化和瘢痕形成
产生滤过手术失败的障碍
VEGF
PIGF
PDGF
FGF
TGF-β
本发明的方法
血液和免疫细胞活化
VEGF
PIGF
PDGF
FGF
内皮细胞增殖
VEGF
PIGF
PDGF
FGF
MMP
成纤维细胞增殖
减少纤维化和瘢痕形成
手术成功率增加
VEGF
PIGF
PDGF
FGF
TGF-β

图1

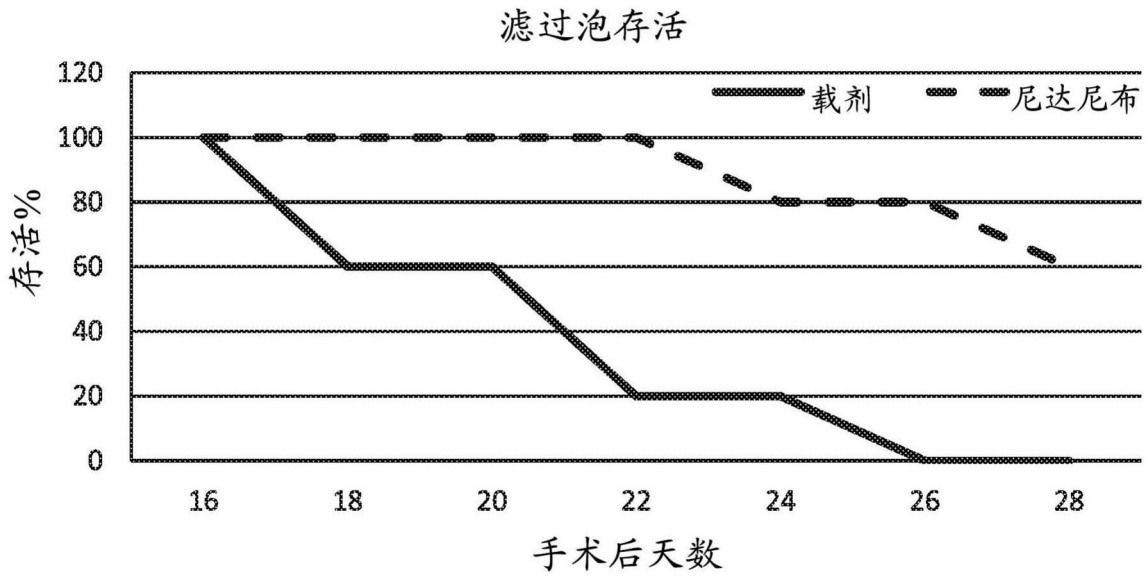

滤过泡存活
120
100
80
60
40
20
0
存活%
载剂
尼达尼布
16
18
20
22
24
26
28
手术后天数

图2

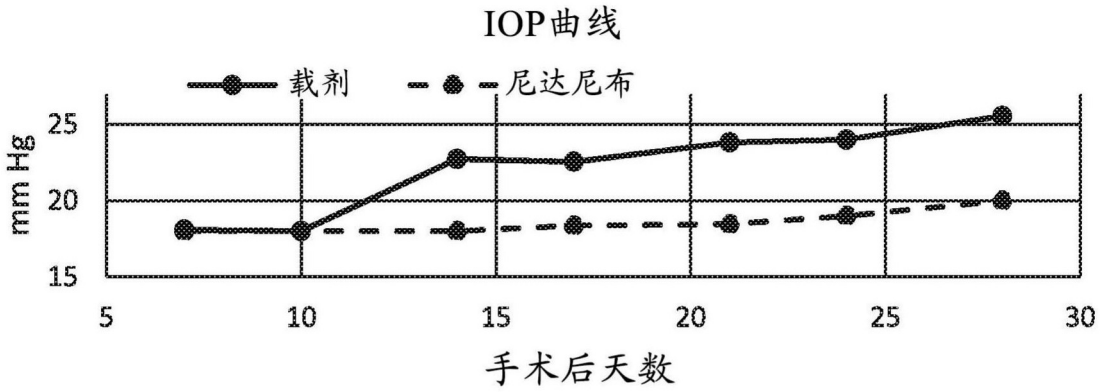

IOP曲线
载剂
尼达尼布
25
20
15
mm Hg
5
10
15
20
25
30
手术后天数

图3

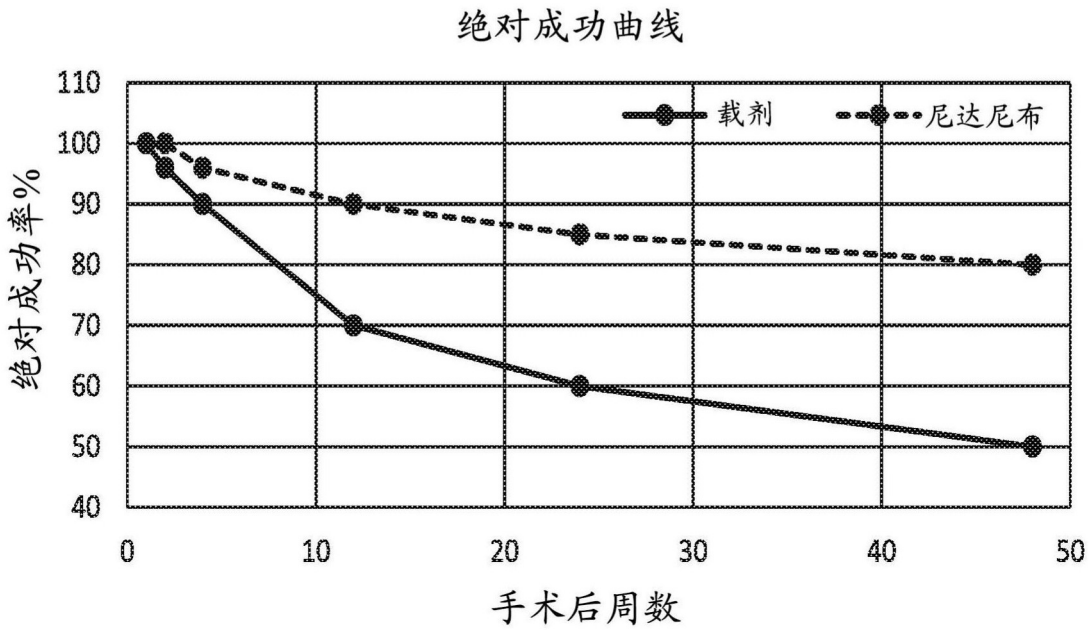

绝对成功曲线
110
100
90
80
70
60
50
40
绝对成功率%
0
10
20
30
40
50
手术后周数
载剂
尼达尼布

图4