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(54) Title: COMPOSITIONS AND METHODS OF USING NINTEDANIB FOR TREATING OCULAR DISEASES WITH ABNORMAL NEOVASCULARIZATION

(57) Abstract: Compositions and methods of using nintedanib for treating indications with abnormal neovascularization in the front part of the eye are disclosed.

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COMPOSITIONS AND METHODS OF USING NINTEDANIB FOR TREATING OCULAR DISEASES WITH ABNORMAL NEOVASCULARIZATION

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 and methods of using nintedanib for the treatment and prevention of graft rejection in high-risk corneal transplant patients, and for the treatment of eye diseases involving abnormal neovascularization in the front part of the eye.

BACKGROUND

Abnormal neovascularization is involved in many diseases in the front part of the eye. Abnormal neovascularization is involved with graft rejection in high-risk corneal transplant patients. Current treatments for many of these indications need improvements. The methods disclosed herein address the problems in current treatments and provide improved treatments for these diseases.

SUMMARY

In certain aspects, the disclosure provides a method for treating eye diseases involving abnormal neovascularization in the front part of the eye, the method comprising an effective amount of administering nintedanib or a pharmaceutically acceptable salt thereof to the eye of a subject in need of such treatment. In certain aspect, the disclosed methods treat, prevent, or delay onset of graft rejection in corneal transplant patients. For example, the disclosed methods treat, prevent, or delay onset of graft rejection in corneal transplant patients with high risk of graft rejection. In certain aspect, the disclosed methods are performed before operation, in

conjunction with operation or after operation, to prevent graft rejection in high-risk corneal transplant.

In certain aspect, nintedanib is administered in the form of 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. 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. In certain aspect, the topical ocular formulation is a solution, a suspension, gel, or an emulsion. In another aspect, nintedanib is administered in the form of 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.

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 schematic diagram demonstrating an exemplary mechanism to prevent graft rejection in high-risk corneal transplant patients according to the present disclosure.

Figure 2A and 2B are graphs demonstrating the reduced cornea neovascularization in the presence of nintedanib in a rabbit cornea suture model. Figure 2A provides results on day 12 and Figure 2B provides results on day 14. The

area of cornea neovascularization are shown for each treatment groups (CBT-1 = nintedanibe ocular formlation: 0.2% CBT-1 BID, 0.2% CBT-1 TID; 0.05% CBT-1 BID, 0.0.5% CBT-1 TID; vehicle control TID. T-test significance levels comparing each group vs vehicle are shown by asterisk symbols.

DETAILED DESCRIPTION

Corneal transplant is a common surgical procedure. Although the overall success of corneal transplant is good, graft failure is still a problem in some high-risk patients. These patients have high inflammation and neovascularization in the host bed that confers increased immune responses and rejection of allograft (Yu et al. World J Transplant. 2016;6(1):10-27). Oral immunosuppressive drugs are sometimes used to reduce the risk of graft failure but they have systemic side effects. The disclosed methods will inhibit vascular endothelial growth factor ("VEGF") and platelet-derived growth factor ("PDGFR") mediated excess neovascularization and attenuate VEGF and fibroblast growth factor ("FGF") related immune responses to prevent graft rejection in high-risk patients. The mechanism is illustrated in Figure 1.

In addition to corneal graft rejection, the disclosed methods can be used to treat any ocular indications involving abnormal neovascularization in the front part of the eye. These indications include graft versus host disease, atopic conjunctivitis, ocular rosacea, ocular pemphigoid, Lyell's syndrome, neovascularization induced by viral, bacterial, fungal, or parasitic infection, contact lens induced neovascularization, ulceration, alkali burns, stem cell deficiency, pinguecula, neovascular glaucoma, dry eye diseases, Sjogren's syndrome, Meibomian gland dysfunction, Steven Johnson syndrome, tumor in the eye.

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 increased corneal neovascularizatoin, etc.) as well as those in which prevention is desired.

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 formulation, 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.

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.

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 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.

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 Cornea Suture Model

The rabbit cornea suture model of neovascularization demonstrates the method's ability to reduce abnormal corneal neovascularization.

Topical ocular formulations

Topical compositions comprising 0.2% or 0.05% nintedanib in 10% 2-hydroxypropyl beta cyclodextrin in phosphate buffer solution, pH 7.4 were prepared.

Animals and treatment procedure

Thirty female Zealand White rabbits were used to perform the study. Briefly, five sutures were placed in the upper cornea of the right eye of each animal on Day 1 to induce neovascularization. The animals were treated in both eyes with either drug, vehicle or saline as described in Table 1.

Table 1

Dosing Period	Group	Treatment	Dosing Frequency	Number of Females
Days 1 to 7	1	Saline	Once daily	6 females
	2	Saline	Once daily	6 females
	3	Saline	Once daily	6 females
	4	Saline	Once daily	6 females
	5	Saline	Once daily	6 females
Days 8 to 15	1	0.2% nintedanib solution	BID	6 females
	2	0.2% nintedanib solution	TID	6 females
	3	0.05% nintedanib solution	BID	6 females
	4	0.05% nintedanib solution	TID	6 females
	5	Saline (OD), Vehicle (OS)	TID	6 females

BID: Twice per day (approximately 10 to 12 hours apart). TID: Three times per day (approximately 6 to 8 hours apart). OD= right eye. OS= left eye.
Both eyes were dosed, the dose volume was approximately 40 µL/eye.
Note: The first dose of saline on Day 1 was done 4 hr post suture placement.

During the study, the animals were closely observed for various ocular indications as well as general physical conditions including body weight. Ocular images were taken on days 7, 10, 12, 14, 21, 28 for analysis of hyperemia.

Data analysis

NIH ImageJ® software was used to analyze the ocular images. Each image was opened in ImageJ®, the scale was calibrated using the ruler in the photograph and the neovascularized area on the cornea near the suture was selected by the selection tool. The area in mm^2 was calculated by measurement tool in the software, recorded in excel and the image was captured and saved. Two-tailed t-TEST was used to determine whether pairs of groups are significantly different. The results were plotted as histograms of average with standard deviation for easy comparison.

Results and discussions

As shown in Figure 2A and 2B, nintedanib had a marked inhibitory effect on suture-induced neovascularization in the rabbit cornea 12 and 14 days after the suture induction. Higher dose of 0.2% nintedanib showed better efficacy than 0.05% nintedanib, while more frequent dosing regimen of TID dosing showed higher efficacy compared with BID dosing.

In summary, nintedanib strongly inhibited corneal neovascularization induced by suture. The strong activity is likely due to the special target profile of nintedanib

that has potent activities against VEGFR1-3 and FGFR1-2. These results support the methods disclosed here.

Example 2: Mouse corneal graft rejection model

In this example, cornea of C57BL/6 mice would be transplanted onto BALB/c mice cornea as described (Sonoda et al. Invest Ophthalmol Vis Sci. 1995 Feb;36(2):427-34; Invest Ophthalmol Vis Sci. 2000 Mar;41(3):790-8.; Yamagami et al. Invest Ophthalmol Vis Sci. 2001 May;42(6):1293-8). The suture would be removed on day 7 after transplant. The mice would be divided into two groups. Group 1 would be treated with the nintedanib 0.2% solution and group 2 with the vehicle solution. Treatment would start immediately after transplant, TID for 8 weeks. The corneal opacity and graft rejection will be assessed weekly for 8 weeks as described.

The nintedanib treated group would show a significantly increased survival of the graft (lower rejection rate) over the 8 weeks of experiment. The result would indicate that the nintedanib 0.2% solution can prevent corneal graft rejection.

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 2.

Table 2 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

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 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 3.

Table 3 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
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 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 4.

Table 4 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 5.

Table 5 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 6.

Table 6 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 treating ocular indications involving abnormal neovascularization, comprising administering to an eye of a subject an effective amount of nintedanib or a pharmaceutically acceptable salt thereof in a form of topical eye drop or implant.

2. The method of claim 1, wherein the indication involving abnormal neovascularization is corneal graft rejection after a high-risk patient received corneal transplant.

3. For the method of claim 1, wherein nintedanib is administered in an amount effective to prevent graft rejection by inhibiting abnormal neovascularization and inflammation in the eye of the subject.

4. The method of claim 1, wherein the indication involving abnormal neovascularization is graft versus host disease.

5. The method of claim 1, wherein the indication involving abnormal neovascularization is atopic conjunctivitis.

6. The method of claim 1, wherein the indication involving abnormal neovascularization is ocular rosacea.

7. The method of claim 1, wherein the indication involving abnormal neovascularization is ocular pemphigoid.

8. The method of claim 1, wherein the indication involving abnormal neovascularization is Lyell's syndrome.

9. The method of claim 1, wherein the indication involving abnormal neovascularization is neovascularization induced by viral, bacterial, fungal, or parasitic infection.

10. The method of claim 1, wherein the indication involving abnormal neovascularization is contact lens induced neovascularization.

11. The method of claim 1, wherein the indication involving abnormal neovascularization is ulceration.

12. The method of claim 1, wherein the indication involving abnormal neovascularization is alkali burns.

13. The method of claim 1, wherein the indication involving abnormal neovascularization is stem cell deficiency.

14. The method of claim 1, wherein the indication involving abnormal neovascularization is pinguecula.

15. The method of claim 1, wherein the indication involving abnormal neovascularization is neovascular glaucoma.

16. The method of claim 1, wherein the indication involving abnormal neovascularization is dry eye diseases.

17. The method of claim 1, wherein the indication involving abnormal neovascularization is Sjogren's syndrome.

18. The method of claim 1, wherein the indication involving abnormal neovascularization is Meibomian gland dysfunction.

19. The method of claim 1, wherein the indication involving abnormal neovascularization is Steven Johnson syndrome.

20. The method of claim 1, wherein the indication involving abnormal neovascularization is tumor in the eye.

21. The method of claim 1, wherein nintedanib is administered in the form of topical ocular formulation or ocular implant

22. The method of claim 21, wherein the ocular implant is in the form of a semi-solid or solid sustained-release implant.

23. The method of claim 22, wherein the implant is injected into the eye eye of the subject.

24. The method of claim 21, wherein the topical ocular formulation is a topical eye drop.

25. The method of claim 21, wherein the topical ocular formulation is a solution, suspension, cream, ointment, gel, gel-forming liquid, suspension containing liposomes or micelles, spray formulation, or emulsion.

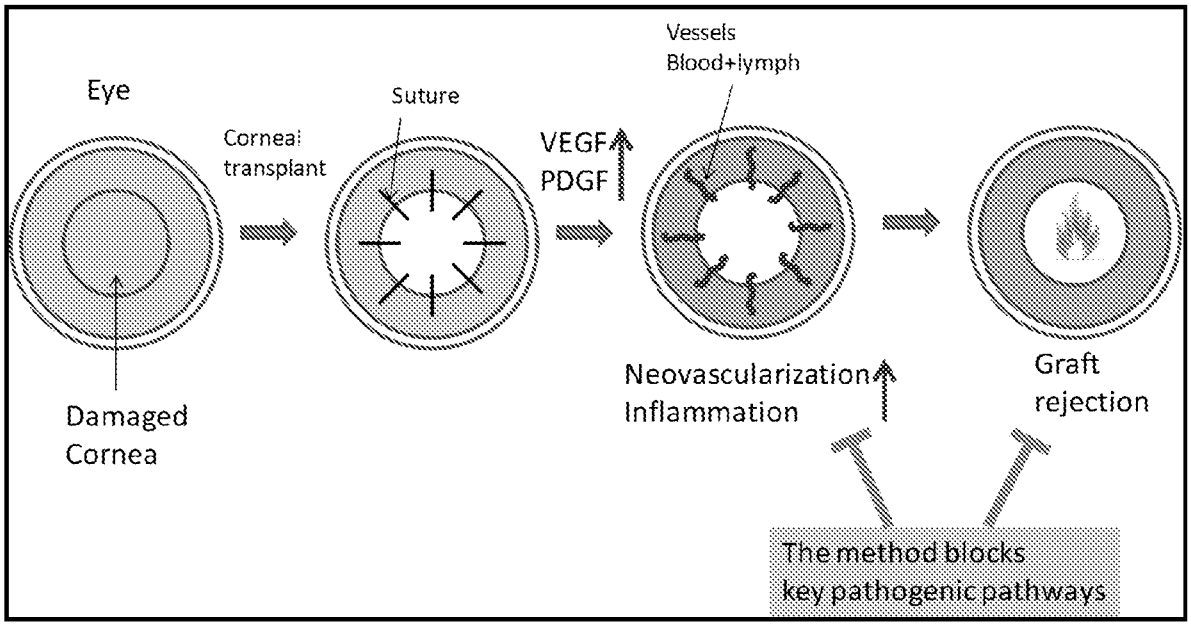
Eye
Corneal transplant
Suture
VEGF
PDGF
Vessels
Blood+lymph
Damaged Cornea
Neovascularization
Inflammation
Graft rejection
The method blocks key pathogenic pathways

Figure 1

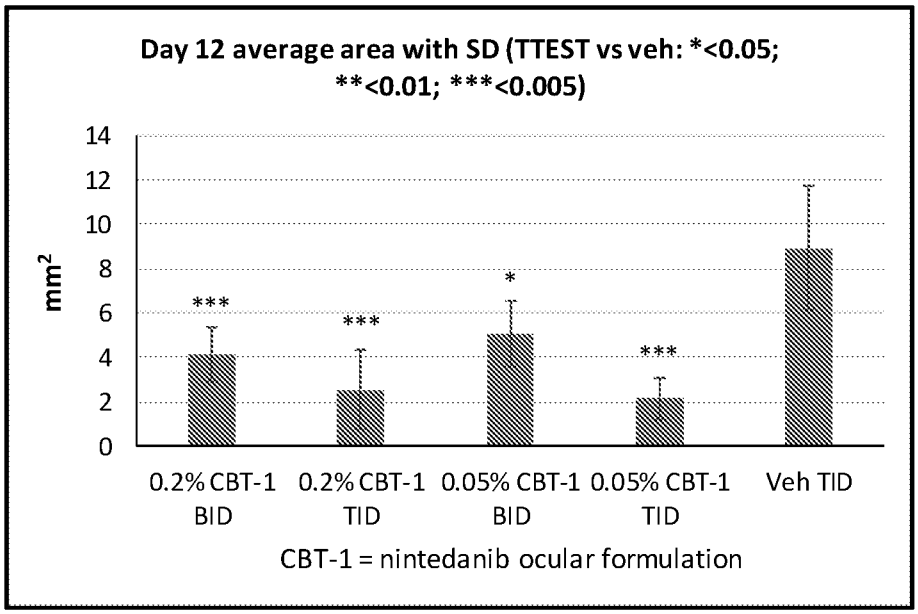

Figure 2A

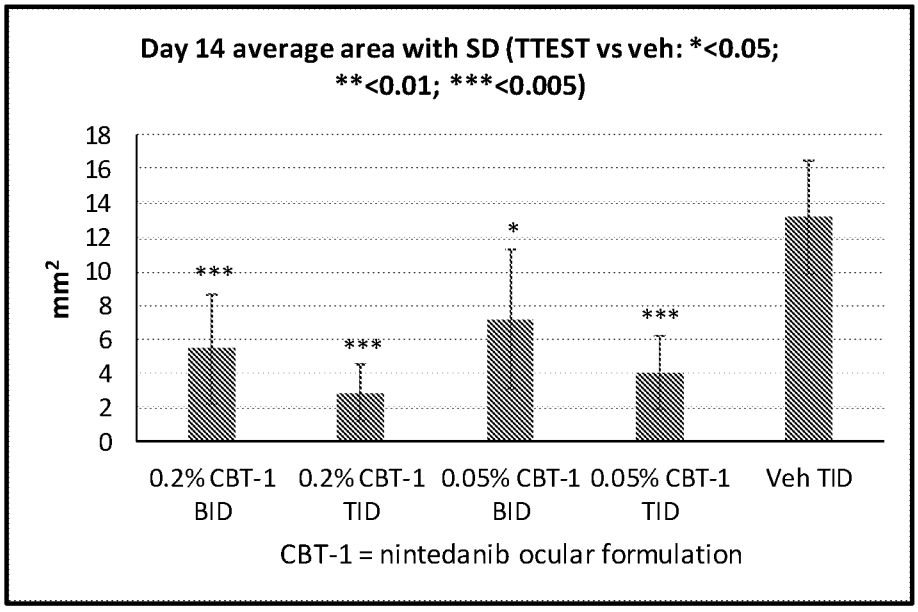

Figure 2B

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US17/34795

A. CLASSIFICATION OF SUBJECT MATTER
IPC - A61K 9/50, 31/506; C07D 209/34 (2017.01)
CPC - A61K 9/5052, 31/506; C07D 209/34

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	(HUU, VAN et al.) 'Light-responsive nanoparticle depot to control release of a small molecule angiogenesis inhibitor in the posterior segment of the eye'; 28 February 2015, Journal of Controlled Release; Volume 200, pages 71-77; abstract; page 7, paragraph [5]; page 8, paragraphs [1]-[2]	1, 21-23 ---------- 2-3, 6, 9, 14-20, 24-25
Y	US 2013/0324481 A1 (RAMSCOR, INC.) 05 December 2013; paragraphs [0024]-[0027]	2-3, 6, 9, 14-20
Y	US 2014/0128395 A1 (FERRARI, G) 08 May 2014; paragraphs [0026], [0037]	4-5, 7-8, 10-13
Y	WO 2014/074823 A1 (CLEARSIDE BIOMEDICAL, INC.) 15 May 2014; paragraphs [0008]-[0009], [0016], [00144], [00173], [00176], [00178], [00214]	24-25
P, X	WO 2016/209555 A1 (ALLGENESIS BIOTHERAPEUTICS INC.) 29 December 2016; entire document	1

☐ 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
"E" earlier application or patent but published on or after the international filing date
"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
28 July 2017 (28.07.2017)	23 AUG 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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C07D 209/34(2006.01)

权利要求书1页 说明书13页 附图2页

(54)发明名称

使用尼达尼布来治疗具有异常新生血管形成的眼病的组合物和方法

(57)摘要

公开了使用尼达尼布来治疗眼前部中具有异常新生血管形成的适应症的组合物和方法。

CN 109475506 A

1.用于治疗涉及异常新生血管形成的眼适应症的方法,其包括以局部滴眼剂或植入物形式对受试者的眼施用有效量的尼达尼布或其药学可接受盐。

2.权利要求1的方法,其中所述涉及异常新生血管形成的适应症是高风险患者接受角膜植入物后的角膜移植物排斥。

3.权利要求1的方法,其中以通过抑制所述受试者眼中的异常新生血管形成和炎症来有效预防移植物排斥的量施用尼达尼布。

4.权利要求1的方法,其中所述涉及异常新生血管形成的适应症是移植物抗宿主病。

5.权利要求1的方法,其中所述涉及异常新生血管形成的适应症是特应性结膜炎。

6.权利要求1的方法,其中所述涉及异常新生血管形成的适应症是眼红斑痤疮。

7.权利要求1的方法,其中所述涉及异常新生血管形成的适应症是眼类天疱疮。

8.权利要求1的方法,其中所述涉及异常新生血管形成的适应症是莱尔氏综合征。

9.权利要求1的方法,其中所述涉及异常新生血管形成的适应症是由病毒性、细菌性、真菌性或寄生性感染诱导的新生血管形成。

10.权利要求1的方法,其中所述涉及异常新生血管形成的适应症是接触镜诱导的新生血管形成。

11.权利要求1的方法,其中所述涉及异常新生血管形成的适应症是溃疡形成。

12.权利要求1的方法,其中所述涉及异常新生血管形成的适应症是碱烧伤。

13.权利要求1的方法,其中所述涉及异常新生血管形成的适应症是干细胞缺乏。

14.权利要求1的方法,其中所述涉及异常新生血管形成的适应症是睑裂斑。

15.权利要求1的方法,其中所述涉及异常新生血管形成的适应症是新生血管性青光眼。

16.权利要求1的方法,其中所述涉及异常新生血管形成的适应症是干眼病。

17.权利要求1的方法,其中所述涉及异常新生血管形成的适应症是干燥综合征(Sjogren's syndrom)。

18.权利要求1的方法,其中所述涉及异常新生血管形成的适应症是睑板腺功能障碍(Meibomian gland dysfunction)。

19.权利要求1的方法,其中所述涉及异常新生血管形成的适应症是斯-琼氏综合征(Steven Johnson syndrome)。

20.权利要求1的方法,其中所述涉及异常新生血管形成的适应症是眼中的肿瘤。

21.权利要求1的方法,其中以局部眼配制剂或眼植入物的形式施用尼达尼布。

22.权利要求21的方法,其中所述眼植入物为半固体或固体持续释放植入物的形式。

23.权利要求22的方法,其中将所述植入物注射到所述受试者的眼中。

24.权利要求21的方法,其中所述局部眼配制剂是局部滴眼剂。

25.权利要求21的方法,其中所述局部眼配制剂是溶液、悬浮液、乳膏、软膏剂、凝胶、凝胶形成性液体、含有脂质体或胶束的悬浮液、喷雾配制剂或乳剂。

使用尼达尼布来治疗具有异常新生血管形成的眼病的组合物和方法

[0001] 优先权要求

[0002] 本申请要求2016年6月2日提交的美国临时专利申请序列号62/344,878和2016年6月2日提交的美国临时专利申请序列号62/344,870的权益,其全部内容通过引用并入本文。

发明领域

[0003] 本公开涉及使用尼达尼布来治疗和预防高风险角膜移植患者中的移植物排斥,以及治疗涉及眼前部中的异常新生血管形成的眼疾病的眼组合物和方法。

[0004] 发明背景

[0005] 异常的新生血管形成是眼前部中的许多疾病牵涉的。异常新生血管形成是高风险角膜移植患者中的移植物排斥中牵涉的。这些中的许多适应症的当前治疗需要改进。本文公开的方法解决当前治疗中的问题并为这些疾病提供改进的治疗方法。

[0006] 发明概述

[0007] 在某些方面,本公开内容提供了治疗涉及眼前部中的异常新生血管形成的眼病的方法,该方法包括对需要此类治疗的受试者的眼施用有效量的尼达尼布(nintedanib)或其药学可接受的盐。在某些方面,所公开的方法在角膜移植患者中治疗、预防移植物排斥或延迟移植物排斥的发作。例如,所公开的方法在具有高移植物排斥风险的角膜移植患者中治疗、预防移植物排斥或延迟移植物排斥的发作。在某些方面,所公开的方法在手术前,结合手术或手术后进行,以防止高角膜移植物风险中的移植物排斥。

[0008] 在某些方面,尼达尼布以局部眼配制剂的形式施用,所述局部眼配制剂对受影响的眼局部施用。在某些方面,配制剂中尼达尼布的浓度为组合物总量的按重量或体积计的0.001%-10%。例如,含水组合物包含0.001%,0.01%,0.1%,0.5%,1.0%,1.5%,2.0%,5.0%或高达10%的尼达尼布。在某些方面,局部眼配制剂是溶液、悬浮液、凝胶或乳剂。另一方面,尼达尼布以注射入受影响的眼中的植入物或半固体持续释放配制剂的形式施用。在某些方面,植入物中尼达尼布的量为1μg至100mg。

[0009] 术语“受试者”是指动物或人,或源自动物或人的一种或多种细胞。优选地,受试者是人。受试者还可包括非人灵长类动物。人受试者可以称为患者。

[0010] 除非另外定义,否则本文使用的所有技术和科学术语具有与本发明所属领域的普通技术人员通常理解的含义相同的含义。本文描述了用于本发明的方法和材料;也可以使用本领域已知的其他合适的方法和材料。材料、方法和实施例仅是说明性的而不意图为限制性的。本文提及的所有出版物、专利申请、专利、序列,数据库条目和其他参考文献通过引用整体并入。若发生冲突,则以本说明书(包括定义)为准。

[0011] 从以下详细说明和附图以及从权利要求书中,本发明的其他特征和优点将显而易见。

[0012] 附图简述

[0013] 图1的示意图表明根据本公开的在高风险角膜移植患者中预防移植物排斥的示例

性机制。

[0014] 图2A和2B的图表明在兔角膜缝合模型中在尼达尼布存在下减少的角膜新生血管形成。图2A提供了第12天的结果，并且图2B提供了第14天的结果。显示了每个处理组的角膜新生血管形成面积(CBT-1＝尼达尼布眼配制剂:0.2％CBT-1BID,0.2％CBT-1TID;0.05％CBT-1BID,0.0.5％CBT-1TID;媒介物对照TID。比较每组与媒介物的T检验显著性水平用星号显示。

[0015] 发明详述

[0016] 角膜移植是一种常见的外科手术。虽然角膜移植的整体成功率良好，但移植失败仍是一些高风险患者的问题。这些患者在宿主床中具有高炎症和新生血管形成，其赋予增强的免疫应答和同种异体移植物排斥(Yu et al.World J Transplant.2016;6(1):10-27)。口服免疫抑制药物有时用于降低移植失败的风险，但它们具有全身副作用。所公开的方法将抑制血管内皮生长因子(“VEGF”)和血小板衍生生长因子(“PDGFR”)介导的过量新生血管形成并减弱VEGF和成纤维细胞生长因子(“FGF”)相关的免疫应答以防止高风险患者中的移植物排斥。机制在图1中显示。

[0017] 在角膜移植物排斥外，公开的方法可以用于治疗任何涉及眼前部中的异常新生血管形成的眼适应症。这些适应症包括移植物抗宿主病、特应性结膜炎、眼红斑痤疮、眼类天疱疮、莱尔氏综合征、由病毒性、细菌性、真菌性或寄生性感染诱导的新生血管形成、接触镜诱导的新生血管形成、溃疡形成、碱烧伤、干细胞缺乏、睑裂斑、新生血管性青光眼、干眼病、干燥综合征(Sjogren's syndrom)、睑板腺功能障碍、斯-琼氏综合征、眼中的肿瘤。

[0018] 术语“治疗/处理”等在本文中通常用于指获得期望的药理学和/或生理学作用。该效果就完全或部分预防疾病或其症状而言可以是预防性的和/或就疾病和/或可归因于疾病的不利影响的部分或完全稳定或治愈而言可以是治疗性的。术语“治疗”包括对哺乳动物，特别是人的疾病的任何治疗，并且包括:(a)预防疾病和/或症状在可能易患疾病或症状但是尚未被诊断为患有疾病或症状的受试者中发生;(b)抑制疾病和/或症状，即阻止其发展;或(c)缓解疾病症状，即引起疾病和/或症状消退。需要治疗的那些受试者包括已经患病的那些受试者(例如，具有增加的角膜新生血管生成的那些手术者等)以及期望预防的那些受试者。

[0019] 尼达尼布{(3Z)-3-{[(4-{甲基[(4-甲基哌嗪-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}(Methyl(3Z)-3-{[(4-{methyl[(4-methylpiperazin-1-yl)acetyl]amino}phenyl)amino](phenyl)methylidene}-2-oxo-2,3-dihydro-1H-indole-6-carboxylate)是如本文所述的激酶抑制剂。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(VEGFR 1-3)、血小板衍生生长因子受体(PDGFRα和β)、成纤维细胞生长因子受体(FGFR1-4)。

[0020] 配制剂和给药方案

[0021] 本文描述的方法包括药物组合物的制备和使用，所述药物组合物包括通过本文描述的方法鉴定为活性成分的化合物。还包括药物组合物本身。

[0022] 药物组合物通常包括药学可接受赋形剂。如本文所用，术语“药学可接受赋形剂”或“药学可接受”包括与药物施用相容的盐水、溶剂、分散介质、包衣材料、抗细菌剂和抗真菌剂、等张剂和吸收延迟剂等。

[0023] 如本文所用、短语“药学可接受盐”是指对于对哺乳动物的施用安全有效且具有期望生物活性的感兴趣化合物的盐。药学可接受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、I 0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(bitartarte)、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、糖二酸盐、甲酸盐、苯甲酸盐、谷氨酸盐、甲磺酸盐、乙磺酸盐(thanesulfonate)、苯磺酸盐、对甲苯磺酸盐和双羟萘酸盐(pamoate)(即I,I’亚乙基-双-(2-羟基-3-萘甲酸))盐。合适的碱盐包括但不限于15铝、钙、锂、镁、钾、钠、锌、铋和二乙醇胺盐。

[0024] 配制合适的药物组合物的方法是本领域已知的,参见,例如Remington:The Science and Practice of Pharmacy,21st ed.,2005;以及Drugs and the Pharmaceutical Sciences:a Series of Textbooks and Monographs(Dekker,NY)系列中的书籍。例如,用于眼科应用的溶液、悬浮液、乳膏、软膏剂、凝胶、凝胶形成性液体、含有脂质体或胶束的悬浮液、喷雾配制剂或乳剂可包括以下组分:无菌稀释剂,例如注射用水、盐水溶液、固定油、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、柠檬酸盐或磷酸盐和调节张力的试剂如氯化钠或右旋糖。可以用酸或碱,例如盐酸或氢氧化钠调节pH。

[0025] 本文公开的药物组合物可包括“治疗有效量”的本文所述的试剂。若使用超过一种试剂,则此类有效量可以基于施用试剂的作用或试剂的组合作用来确定。试剂的治疗有效量也可随诸如疾病状态、个体的年龄、性别和体重以及化合物在个体中引发期望应答,例如改善至少一种病症参数或改善至少一种病症症状的能力等因素而变化。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。

[0026] 用于治疗状况的本公开组合物的有效剂量随许多不同因素而变化,包括施用方式、靶位点、受试者的生理状态、受试者是人还是动物、施用的其他药物、和治疗是预防还是治疗。可以使用本领域技术人员已知的常规方法滴定治疗剂量以优化安全性和功效。

[0027] 适于注射使用的药物组合物可包括无菌水溶液(在水溶性的情况下)或分散体和用于临时制备无菌可注射溶液或分散体的无菌粉末。它应当在制造和储存条件下稳定,并且必须针对微生物如细菌和真菌的污染作用提供防护。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),以及它们的合适混合物。例如,可以通过使用诸如卵磷脂的涂层材料,通过在分散体的情况下维持需要的粒度以及通过使用表面活性剂来维持适当的流动性。可以通过各种抗细菌剂和抗真菌剂,例如对羟基苯甲酸酯、氯丁醇、酚、抗坏血酸、硫柳汞等防止微生物的作用。在许多情况下,优选在组合物中包含等张剂,例如糖、多元醇如甘露醇、山梨糖醇和氯化钠。可以通过在组合物中包括延迟吸收的试剂,例如单硬脂酸铝和明胶来实现可注射组合物的延长吸收。

[0028] 无菌可注射溶液可以通过将需要量的活性化合物掺入具有上面列举的成分中的一种或组合(如果需要的话)的适当的溶剂中,然后过滤灭菌来制备。通常,通过将活性化合物掺入无菌媒介物中来制备分散体,所述无菌媒介物含有基础分散介质和来自上面列举的那些成分的需要的其他成分。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,它们从先前无菌过滤的溶液中产生活性成分和任何其他期

望成分的粉末。

[0029] 在一个实施方案中，治疗性化合物用载体制备，所述载体将保护治疗性化合物免于从体内快速消除，例如受控释放配制剂，包括植入物和微囊化递送系统。可以使用可生物降解的、生物相容的聚合物，例如乙烯乙酸乙烯酯(ethylene vinyl acetate)、聚酐、聚乙醇酸、胶原、聚原酸酯和聚乳酸。此类配制剂可使用标准技术制备，或商购获得。

[0030] 药物组合物可以与施用说明一起包含在容器、包装或分配器中。

[0031] 尼达尼布的组合物和配制剂可以局部施用或作为半固体配制剂或固体植入物的注射施用，或通过本领域已知的任何其它合适的方法施用。尽管可以使用本文公开的试剂本身进行治疗，但优选将试剂作为药物配制剂施用，例如，与就意图的施用路径和标准药学实践而言选择的合适的药物赋形剂、稀释剂或载体混合。药物配制剂包括至少一种活性化合物，以及药学可接受的赋形剂、稀释剂和/或载体。

[0032] 组合物或配制剂的施用可以是一天一次、一天两次、一天三次、一天四次或更频繁。可以在治疗的治疗维持阶段期间降低频率，例如，每两天一次或每三天一次，而不是每天一次或每天两次。剂量和施用频率可以根据治疗医师的判断进行调整，例如，考虑到用本方法治疗的状况的疾病的临床体征、病理体征和临床和亚临床症状，以及患者的临床病史。

[0033] 应当理解，本文公开的用于治疗需要的试剂量将随施用途径、需要治疗的状况的性质以及患者的年龄、体重和状况而变化，并且最终由主治医师决定。组合物通常含有有效量的尼达尼布。可以根据动物试验确定初步剂量，并且可以根据本领域公认的实践进行人类施用剂量的缩放。

[0034] 治疗时间(即天数)将由治疗受试者的医师容易地确定；然而，治疗天数的范围可以是约1天至约365天。如本方法所提供的，可以在治疗过程期间监测治疗功效，以确定治疗是否成功，或者是否需要额外的(或修改的)治疗。

[0035] 治疗化合物的剂量、毒性和治疗功效可通过细胞培养物或实验动物中的标准药学程序(例如用于测定LD50(对50％群体致死的剂量)和ED50(50％的群体中治疗有效的剂量))测定。尼达尼布的剂量形式可以由普通技术人员容易地确定，并且可以例如在动物模型和文献中报道的临床研究中获得，用于根据本领域已知的标准方法确定剂量、安全性和功效。确切的配方、施用途径和剂量可以由个别医师根据患者的病情选择。

[0036] 用于本方法的组合物可以以组合物总量的按重量或体积计0.001％-10％的浓度包含尼达尼布。例如，含水组合物包含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。

[0037] 如本领域技术人员所熟知的，水溶液对眼的施用可以是来自点滴器或移液管或其他专用无菌装置的(例如尼达尼布溶液)“滴剂”或多个“滴剂”的形式。此类液滴的体积通常高达50微升，但是可以更小，例如小于10微升。

实施例

[0038] 在以下实施例中进一步描述本发明，这些实施例不限制权利要求书中描述的本发明的范围。

[0039] 实施例1：兔角膜缝合模型

[0040] 新生血管形成的兔角膜缝合模型证明该方法减少异常角膜新生血管形成的能力。

[0041] 局部眼配制剂

[0042] 制备包含磷酸盐缓冲溶液(pH7.4)中10％2-羟丙基β环糊精中的0.2％或0.05％尼达尼布的局部组合物。

[0043] 动物和治疗程序

[0044] 使用30只雌性西兰白兔(Zealand White rabbit)进行研究。简言之,在第1天将5个缝线置于每只动物的右眼的上角膜中以诱导新生血管形成。如表1中所述,用药物、媒介物或盐水在两只眼睛中处理动物。

[0045] 表1

[0046]

给药期	组	处理	给药频率	雌性数目
第1-7天	1	盐水	一天一次	6只雌性
	2	盐水	一天一次	6只雌性
	3	盐水	一天一次	6只雌性
	4	盐水	一天一次	6只雌性
	5	盐水	一天一次	6只雌性
第8-15天	1	0.2%尼达尼布溶液	BID	6只雌性
	2	0.2%尼达尼布溶液	TID	6只雌性
	3	0.05%尼达尼布溶液	BID	6只雌性
	4	0.05%尼达尼布溶液	TID	6只雌性
	5	盐水(OD),媒介物(OS)	TID	6只雌性

[0047] BID:每天两次(相隔约10至12小时)。TID:每天三次(相隔约6至8小时)。OD＝右眼。OS＝左眼。

[0048] 对双眼给药,剂量体积为约40μL/眼。

[0049] 注意:第1天的第一剂盐水在缝线放置后4小时完成。

[0050] 在研究期间,密切观察动物的各种眼适应症以及包括体重在内的一般身体状况。在第7天、第10天、第12天、第14天、第21天、第28天拍摄眼图像用于分析充血。

[0051] 数据分析

[0052] NIHImageJ®软件用于分析眼图像。每个图像在ImageJ®中打开,使用照片中的标尺校准刻度,并且通过选择工具选择缝线附近的角膜上的新生血管化区域。以mm^2计的面积由软件中的测量工具计算,在excel中记录,捕获并保存图像。双因素t-TEST用于确定成对的组是否显著不同。将结果绘制为平均值与标准偏差的直方图以便于比较。

[0053] 结果与讨论

[0054] 如图2A和2B所示,尼达尼布在缝线诱导后12和14天对兔角膜中的缝线诱导的新生血管形成具有显著的抑制作用。较高剂量的0.2％尼达尼布显示出比0.05％尼达尼布更好的疗效,而TID给药的更频繁的给药方案与BID给药相比显示出更高的疗效。

[0055] 总之,尼达尼布强烈抑制缝线诱导的角膜新生血管形成。强烈的活性可能是由于

针对VEGFR1-3和FGFR1-2具有有力活性的尼达尼布的特殊目标概貌。这些结果支持本文公开的方法。

[0056] 实施例2:小鼠角膜移植物排斥模型

[0057] 在该实施例中,如(Sonoda et al.Invest Ophthalmol Vis Sci.1995Feb;36(2):427-34;Invest Ophthalmol Vis Sci.2000Mar;41(3):790-8.;Yamagami et al.Invest Ophthalmol Vis Sci.2001May;42(6):1293-8)所描述的,将C57BL/6小鼠的角膜移植到BALB/c小鼠角膜上。移植后第7天将切除缝合线。将小鼠分成两组。第1组用尼达尼布0.2%溶液处理,并且第2组用媒介物溶液处理。移植后立即TID开始处理8周。如上所述,将每周评估角膜混浊和移植物排斥,达8周。

[0058] 尼达尼布处理组在8周的实验内显示出移植物的存活率显著增加(较低的排斥率)。结果指示尼达尼布0.2%溶液可以防止角膜移植物排斥。

[0059] 实施例3:配制剂

[0060] 尼达尼布眼溶液

[0061] 药物产品是在2-羟丙基β环糊精或其他类似的环糊精和缓冲溶液中制备的等张眼溶液,pH范围为5.5至8.0。可以加入其他粘度、润滑剂、防腐剂以增强配制剂的功能性。眼溶液的组成在表2中公开。

[0062] 表2尼达尼布眼溶液

[0063]

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	粘度剂/干眼舒缓剂	0 – 1
Pemulen TR	粘度剂	0 – 0.2
聚乙烯醇	粘度/润滑剂	0 – 1.5
羟丙甲纤维素(Hypromellose)	润滑剂/干眼舒缓剂(dry eye relief)	0 - 1
卡波姆	润滑剂/干眼舒缓剂	0 – 0.5
羧甲醚纤维素钠	润滑剂/干眼舒缓剂	0 – 1
玻璃酸钠	润滑剂/干眼舒缓剂	0 – 1.5
聚乙二醇400	润滑剂/干眼舒缓剂	0 – 0.4
丙二醇	润滑剂/干眼舒缓剂	0 – 0.6

[0064]

成分	功能	浓度范围 (%w/v)
2-羟丙基beta 环糊精	增溶剂	0 - 10
硫代丁基(Sulfobutyl)-beta-环糊精	增溶剂	0 - 10
随机甲基化beta-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
Poloxamer 188 或 237 或407	增溶剂/润滑剂	0 – 5
Polysorbate 80	增溶剂/润滑剂/表面活性剂	0 – 1
依地酸二钠	螯合剂/防腐剂	0 – 0.01
苯扎氯铵	防腐剂	0 – 0.02
磷酸二氢钠一水合物	缓冲剂	0 – 0.43
磷酸氢二钠七水合物	缓冲剂	0 – 0.8
硼酸	缓冲剂	0 – 0.6
硼酸钠，十水合物	缓冲剂	0 – 0.045
柠檬酸，一水合物	缓冲剂/防腐剂	0 – 0.13
柠檬酸钠，二水合物	缓冲剂/防腐剂	0 – 0.45
丙三醇	张力剂	0 – 2.2
氯化钠	张力剂	0 – 0.83
1N氢氧化钠	pH调节	pH 5.5 – 8.0
1N盐酸		
注射用水	媒介物	Q.S.至100

[0065] 尼达尼布眼悬浮液

[0066] 药物产品是在羧甲基纤维素钠和缓冲溶液中制备的等张眼悬浮液，pH范围为5.5至8.0。药物颗粒尺寸减小到40微米以下。可加入其他粘度、润滑剂、增溶剂和防腐剂以增强配制剂悬浮液的功能。该组合物公开于表3中。

[0067] 表3尼达尼布眼悬浮液

[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

[0069]

成分	功能	浓度范围 (%w/v)
羧甲基纤维素钠	粘度剂/干眼舒缓剂	0 – 1
Pemulen TR	粘度剂	0 – 0.2
聚乙烯醇	粘度/润滑剂	0 – 1.5
羟丙甲纤维素	润滑剂/干眼舒缓剂	0 - 1
卡波姆	润滑剂/干眼舒缓剂	0 – 0.5
羧甲醚纤维素钠	润滑剂/干眼舒缓剂	0 – 1
玻璃酸钠	润滑剂/干眼舒缓剂	0 – 1.5
聚乙二醇400	润滑剂/干眼舒缓剂	0 – 0.4
丙二醇	润滑剂/干眼舒缓剂	0 – 0.6
2-羟丙基beta 环糊精	增溶剂	0 - 10
硫代丁基-beta-环糊精	增溶剂	0 - 10
随机甲基化beta-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
Poloxamer 188 或 237 或407	增溶剂/润滑剂	0 – 5
Polysorbate 80	增溶剂/润滑剂/表面活性剂	0 – 1
依地酸二钠	螯合剂/防腐剂	0 – 0.01
苯扎氯铵	防腐剂	0 – 0.02
磷酸二氢钠一水合物	缓冲剂	0 – 0.43
磷酸氢二钠七水合物	缓冲剂	0 – 0.8
硼酸	缓冲剂	0 – 0.6
硼酸钠，十水合物	缓冲剂	0 – 0.045
柠檬酸，一水合物	缓冲剂/防腐剂	0 – 0.13
柠檬酸钠，二水合物	缓冲剂/防腐剂	0 – 0.45
丙三醇	张力剂	0 – 2.2
氯化钠	张力剂	0 – 0.83
1N氢氧化钠	pH调节	pH 5.5 – 8.0
1N盐酸		
注射用水	媒介物	Q.S.至100

[0070] 尼达尼布眼乳液

[0071] 药物产品是等张眼乳液。将药物溶解在混合物油相和乳化剂赋形剂中，然后将其

乳化并与pH范围为5.5-8.0的水相混合。可以加入其他粘度、润滑剂、增溶剂和防腐剂以增强乳剂配制剂的功能。该组合物公开于表4中。

[0072] 表4尼达尼布眼乳剂

[0073]

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
Polyoxyl-40-Stearate	乳化剂	0 – 0.25
Polysorbate 80	增溶剂/乳化剂/表面活性剂	0 - 1
硫代丁基-β-环糊精	增溶剂	0 - 5
2-羟丙基-beta-环糊精	增溶剂	0 - 5
随机甲基化beta-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
丙三醇	张力剂	0 - 2.2
氯化钠	张力剂	0 – 0.83
Pemulen TR2	粘度剂	0 – 0.1
羧甲基纤维素钠	粘度剂	0 – 0.5
聚乙烯醇	粘度/润滑剂	0 – 1.5
羟丙甲纤维素	润滑剂/干眼舒缓剂	0 - 1
卡波姆	润滑剂/干眼舒缓剂	0 – 0.5
羧甲醚纤维素钠	润滑剂/干眼舒缓剂	0 – 1
玻璃酸钠	润滑剂/干眼舒缓剂	0 – 1.5
聚乙二醇400	润滑剂/干眼舒缓剂	0 – 0.4
丙二醇	润滑剂/干眼舒缓剂	0 – 0.6
Poloxamer 188 或 237 或407	增溶剂/润滑剂	0 – 5
硼酸	缓冲液	0 – 0.6
硼酸钠，十水合物	缓冲液	0 – 0.045
柠檬酸，一水合物	缓冲液/防腐剂	0 – 0.13
柠檬酸钠，二水合物	缓冲液/防腐剂	0 – 0.45
磷酸二氢钠一水合物	缓冲液	0 – 0.43
磷酸氢二钠七水合物	缓冲液	0 – 0.8
1N & 5N氢氧化钠	pH调节	pH 5.5 – 8.0
1N盐酸		
注射用水	水性媒介物	Q.S. 100

[0074] 尼达尼布持续释放半固体配制剂

[0075] 药物产品是等张持续释放半固体配制剂。将药物溶解和/或悬浮在pH范围为5.5至8.0的半固体培养基中。可以加入其他粘度、润滑剂、增溶剂和防腐剂以增强持续释放半固体配制剂的功能。该组合物公开于表5中。

[0076] 表5持续释放半固体配制剂

[0077]

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	粘度/增稠剂	0 - 10
羟丙基甲基纤维素	粘度/增稠剂	0 – 10
玻璃酸钠	粘度/增稠剂	0 – 5
透明质酸	粘度/增稠剂	0 - 5
硼酸	缓冲液	0 – 0.6
硼酸钠, 十水合物	缓冲液	0 – 0.045
柠檬酸, 一水合物	缓冲液/防腐剂	0 – 0.13
柠檬酸钠, 二水合物	缓冲液/防腐剂	0 – 0.45
磷酸二氢钠一水合物	缓冲液	0 – 0.43
磷酸氢二钠七水合物	缓冲液	0 – 0.8
1N & 5N氢氧化钠	pH调节	pH 5.5 – 8.0
1N盐酸		
注射用水	水性媒介物	Q.S. 100

[0078] 尼达尼布持续释放植入物

[0079] 药物产品是固体植入物。将药物混合并与一种或多种聚合物混合。药物和聚合物的混合物在预定温度下熔化并挤出成具有预定直径尺寸的长丝。将配制剂细丝切成预定大小的片段,该片段可以植入眼组织中。该组合物公开于表6中。

[0080] 表6持续释放植入物

[0081]

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-丙交酯), i.v. 0.25-0.35 dL/g	聚合物	0 – 100

[0082]

成分	功能	浓度 (% w/w)
聚(D,L-丙交酯-共乙交酯) i.v. 0.14-0.22 dL/g	聚合物	0 – 100
聚(D,L-丙交酯), 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

[0083] 非限制性地,可以从现有的眼科上可接受的组合物中修改用于根据本发明的方法的示例性组合物。

[0084] 其他实施方案

[0085] 应当理解,虽然已经结合本发明的详细描述描述了本发明,但是前面的描述旨在说明而不是限制本发明的范围,本发明的范围由所附权利要求书的范围限定。其他方面、优点和修改在所附权利要求书的范围内。

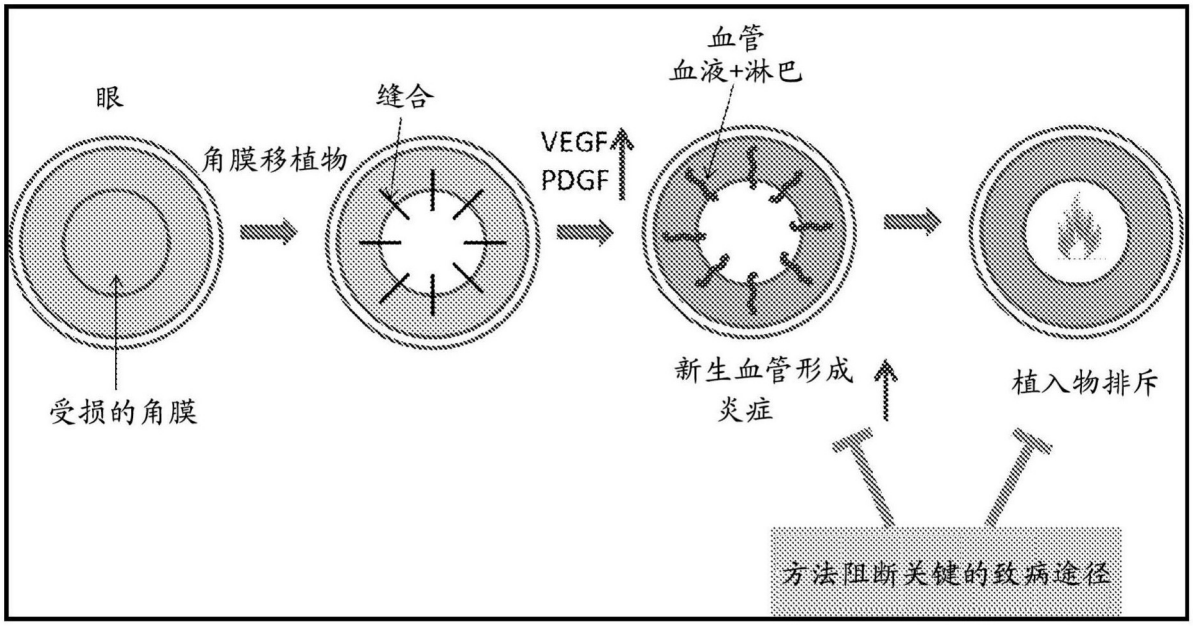
眼
角膜移植物
缝合
VEGF
PDGF
血管
血液+淋巴
受损的角膜
新生血管形成
炎症
植入物排斥
方法阻断关键的致病途径

图1

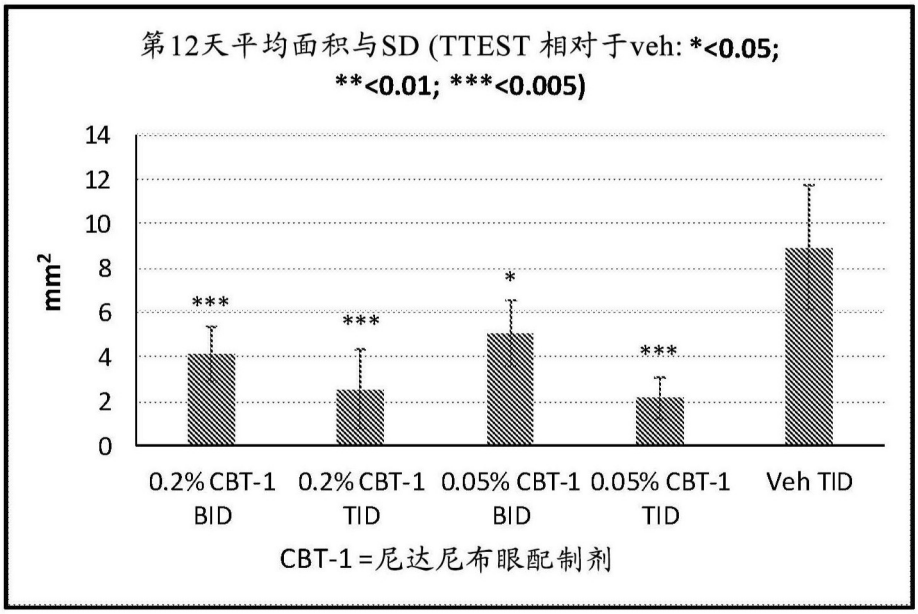
第12天平均面积与SD (TTEST 相对于veh: *<0.05; **<0.01; ***<0.005)
mm²
14
12
10
8
6
4
2
0
***
***
*
***
0.2% CBT-1 BID
0.2% CBT-1 TID
0.05% CBT-1 BID
0.05% CBT-1 TID
Veh TID
CBT-1 =尼达尼布眼配制剂

图2A

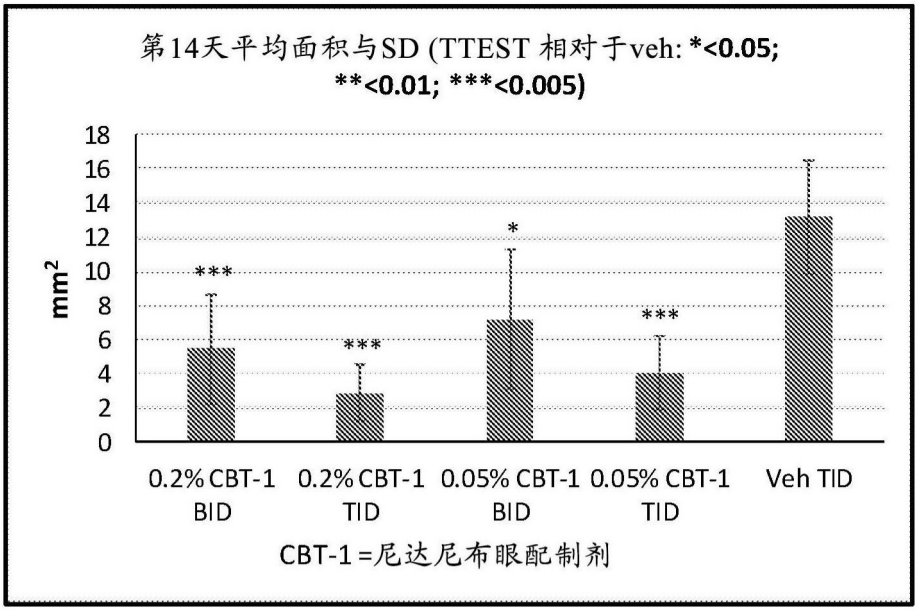
第14天平均面积与SD (TTEST 相对于veh: *<0.05; **<0.01; ***<0.005)
mm2
18
16
14
12
10
8
6
4
2
0
***
***
*
***
0.2% CBT-1 BID
0.2% CBT-1 TID
0.05% CBT-1 BID
0.05% CBT-1 TID
Veh TID
CBT-1 =尼达尼布眼配制剂

图2B