PHARMACEUTICALS FOR TREATMENT OF VIRAL INFECTIONS OF THE EYE

Background of the Invention

The invention relates to viral infections of the eye, and more particularly relates to methods and pharmaceuticals for treatment of viral infections of the eye. In its most immediate sense, the invention relates to treatment of human eye infections caused by *Herpesviridae* viruses (including but not limited to *Human cytomegalovirus, herpes zoster* virus, *and varicella zoster* virus) and *Adenoviridae* viruses.

Viral diseases of the eye can have significant consequences. Type 1 *herpes simplex* virus can cause conjunctivitis and keratitis, *Human cytomegalovirus* can cause retinitis, *adenovirus* types 8, 19, 29, and 37 can cause epidemic keratoconjunctivitis, and *adenovirus* types 3, 4, and 7 can cause pharyngoconjuctival fever. *Herpes zoster* virus (HZV), a member of the *Herpesviridae* family, can cause severe eye disease when affecting the trigeminal area. Herpes zoster ophthalmicus, a severe form of acute herpes zoster, results from the reactivation of *varicella zoster* virus (VZV) (another member of the *Herpesviridae* family) in the trigeminal (fifth cranial) nerve. Any branch of the nerve may be affected, though the frontal branch within the first division of the trigeminal nerve is most commonly involved. This frontal branch innervates nearly all of the ocular and periocular structures. Herpes zoster ophthalmicus at this particular location can lead to blindness and requires a fast and effective therapeutic approach.

Human cytomegalovirus (CMV) is another member of the *Herpesviridae* family. At least 60% of the US population has been exposed to CMV, with a prevalence of more than 90% in high-risk groups (e.g., unborn babies whose mothers become infected with CMV during pregnancy, people with HIV, and transplant recipients).

CMV retinitis is one of the most common opportunistic infections in persons with AIDS or pharmacologically induced immunosuppression. Individuals with CMV retinitis typically exhibit a progressive decrease in visual acuity, which may progress to blindness. Long-term CMV treatment is necessary to prevent retinitis relapse.

Immune reconstitution syndrome (IRIS) is reported in 16%-63% of HIV-infected patients with CMV retinitis following the initiation of HAART (Highly

Active Antiretroviral Treatment). CMV IRIS may manifest as painless floaters, blurred vision, photopia, decreased visual acuity, or ocular pain. Some patients may develop macular edema leading to vision loss or proliferative vitreoretinopathy, spontaneous vitreal hemorrhage, and retinal detachment.

It is known to treat viral eye infections with acyclovir but such treatment is not entirely satisfactory. Topical acyclovir must be applied frequently and causes irritation of the eye. Oral acyclovir causes significant adverse side effects. Other antiviral medications such as gancyclovir, valacyclovir and valgancyclovir are used to treat viral eye infections, and such treatments are also not entirely satisfactory. Gancyclovir is administered intravenously, and therefore cannot be used outside e.g. a hospital setting. Oral antiviral medications such as valacyclovir and valgancyclovir have disadvantages; they are known to cause fever, rash, diarrhea, and hematologic effects (e.g., neutropenia, anemia, thrombocytopenia). In some cases neutropenia may respond to lowering the dose or using drugs that stimulate the production of neutrophils by the bone marrow as granulocyte colony-stimulating factor [G-CSF], or granulocyte-macrophage colony-stimulating factor [GM-CSF]. These toxic effects can be difficult to manage.

It would therefore be advantageous to provide a better method and a better pharmaceutical for treating viral eye infections in humans.

Various enzymatically active ribonucleases, including ranpirnase and other proteins that are highly homologous to it, are known to have antiviral activity, and to have activity against viruses in the *Herpesviridae* family (specifically including but not limited to *Herpes simplex* virus types 1 and 2 and *Human cytomegalovirus*) and also against type 2 *adenovirus*. However, proteins are known to be highly irritating to the eye due to an intense inflammatory response mediated by T-cells. For this reason, although ranpirnase and other related proteins have been investigated for use against various viral infections, they have not been investigated for use against viral infections of the eye.

Despite the expectation that proteinaceous ranpirnase would cause irritation in the eye, irritation of topically applied ranpirnase in the eye was studied in a rabbit model. In this experiment, ranpirnase was demonstrated to be non-irritating as determined using the Globally Harmonized System of Classification Evaluation Criteria and the European Economic Community Ocular Evaluation Criteria. This

was a remarkable result, because administration of a foreign protein to the eye can produce corneal irritation. As a result, ranpirnase and other proteins that are highly homologous to it are expected to be useful in treating viral diseases of the human eye.

Brief Description of the Drawings

The invention will be better understood with reference to the following exemplary and non-limiting drawings, in which:

Fig. 1 shows the scale used for scoring ocular lesions observed in a rabbit that has undergone a Draize test;

Fig. 2 shows the results of a Draize test in which a ranpirnase solution was applied to the right eye of three rabbits;

Fig. 3 shows the results of the Draize test of Fig. 2 in which the left eye of each of the rabbits was untreated; and

Fig. 4 shows the European Economic Community Ocular Evaluation Criteria used to classify the ocular irritation caused by a test article in a Draize test.

Detailed Description of Preferred Embodiments

Ranpirnase is a proteinaceous enzymatically active ribonuclease that is disclosed and claimed in U.S. Patent No. 5,559,212. U.S. Patents Nos. 5,728,805, 6,239,257, 7,229,824 and US 8,518,399 disclose three other proteinaceous enzymatically active ribonucleases that are highly homologous to ranpirnase:

a) the RNase of SEQ ID NO:2 in U.S. Patent No. 5,728,805, herein referred to as the "'805 variant";
b) the RNase of SEQ ID NO:2 in Patent No. US 6,239,257, herein referred to as "Amphinase 2", and;
c) the RNase of SEQ ID NO:59 of Patent No. US 7,229,824, herein referred to as "rAmphinase 2".

Patent No. US 8,518,399 discloses that ranpirnase, the '805 variant, and rAmphinase 2 have antiviral activity against *Herpesviridae* viruses, specifically including but not limited to *Herpes simplex* types 1 and 2 and *Human*

cytomegalovirus. Based upon its similarities with these three enzymatically active ribonucleases, it is believed that Amphinase 2 will have these activities as well.

Further, international patent application WO 2015/148768 A2 discloses that ranpirnase has antiviral activity against a number of viruses, including type 2 *adenovirus*.

RNases of the RNase A superfamily are pyrimidine-specific endonucleases found in high quantity in the pancreas of certain mammals and of some reptiles. They are involved in endonucleolytic cleavage of 3'-phosphomononucleotides and 3'-phosphooligonucleotides ending in C-P or U-P with 2',3'-cyclic phosphate intermediates. Members of this superfamily include ranpirnase and variants thereof, amphinase, r-Amphinase-2, bovine seminal vesicle and brain ribonucleases; kidney non-secretory ribonucleases; liver-type ribonucleases, angiogenin; eosinophil cationic protein, and pancreatic ribonucleases from different species including human and bovine pancreatic ribonucleases.

Ranpirnase is an RNase isolated from oocytes of the leopard frog *Rana pipiens* which is disclosed in U.S. Pat. No. 5,559,212, and was formerly known as ONCONASE®. The amino acid sequence of ranpirnase is provided in SEQ ID NO: 1. Ranpirnase has been tested and found to be cytotoxic to cancer cells because of its enzymatic activity against RNA.

A variant of ranpirnase is disclosed in U.S. Pat. No. 5,728,805 (hereinafter, the "'805 variant"). The '805 variant is also an RNase, and has likewise been found to be cytotoxic to certain cancer cells. The '805 variant is a close variant of ranpirnase; its amino acid sequence is identical to that of ranpirnase except that it has valine instead of isoleucine at position 11, asparagine instead of aspartic acid at position 20, and arginine instead of serine at position 103 of the ranpirnase amino acid sequence. In some embodiments, the '805 variant is referred to as "Val11, Asn20, Arg103-Ranpirnase". The amino acid sequence of the '805 variant is provided in SEQ ID NO:2.

Amphinase 2 is also an RNase. It is the protein identified as 2325p4 in U.S. Pat. No. 6,239,257 and it too has been found to be cytotoxic to cancer cells. The amino acid sequence of Amphinase 2 is provided in SEQ ID NO: 3.

Recombinant Amphinase 2 ("rAmphinase 2") is similar to Amphinase 2, but has a Met residue at position −1 and lacks glycan moieties that are located in

Amphinase 2 at positions 27 and 91. rAmphinase 2 is described in U.S. Pat. No. 7,229,824. The amino acid sequence of rAmphinase 2 is provided in SEQ ID NO: 4.

The term "functionally equivalent thereof" is intended to comprise proteins which differ from any naturally occurring RNase by the deletion, addition or substitution of one or more amino acids, but retain RNase activity. For example, the '805 variant discussed above may be considered as a functional derivative of ranpirnase, because it comprises three amino acid substitutions compared to the ranpirnase amino acid sequence, but still has RNase activity.

In one embodiment the term "RNase of the RNase A superfamily" also includes fusion proteins of the RNase, in particular ranpirnase, with another protein such as an antibody or antibody fragment. Such a fusion protein is described in WO 2005/080586 A1. In an alternative embodiment the term "RNase of the RNase A superfamily" does not include such fusion proteins, meaning that the RNase is the only active protein which is used for the treatment of a viral infection of the eye.

U.S. Pat. Nos. 5,559,212, 5,728,805, 6,239,257, 7,229,824, 8,518,399, 8,663,964, and U.S. Publication Nos. 2012-0003266 and 2014-0037610 are all incorporated by reference herein in their entireties for all purposes.

As discussed before it has been found that an RNase of the RNase A superfamily, in particular ranpirnase, can be used in the treatment of a viral disease of the eye. "Viral diseases of the eye" are diseases which show symptoms predominantly in the eye of a subject and which are caused by viruses and not by bacteria. Symptoms of eye diseases include itching, excessive watering, red or pink color of the conjunctiva, pain, dry eyes, light sensitivity, swollen eyes, eye discharge and blurry vision. Viral diseases of the eye include, but are not limited to, conjunctivitis and keratitis, chorioretinitis, retinitis, keratoconjunctivitis, pharyngoconjuctival fever and CMV retinitis.

Viral conjunctivitis, also known as pink eye, is characterized by inflammation of the outermost layer of the white part of the eye and the inner surface of the eyelid. It makes the eye appear pink or reddish. There may also be pain, burning, scratchiness, or itchiness. Viral conjunctivitis is typically caused by adenovirus. Other viruses that can be responsible for conjunctival infection include herpes simplex virus (HSV), varicella-zoster virus (VZV), enterovirus 70, Coxsackie virus A24, molluscum contagiosum and human immunodeficiency virus (HIV).

Viral keratitis is an inflammation of the cornea which is predominantly caused by herpes simplex virus. This condition is often accompanied by moderate to intense pain and usually involves one or more of the following symptoms: pain, impaired eyesight, photophobia and red eye.

Chorioretinitis is an inflammation of the choroid (thin pigmented vascular coat of the eye) and retina of the eye. It is a form of posterior uveitis. Symptoms may include the presence of floating black spots, blurred vision, pain or redness in the eye, sensitivity to light, or excessive tearing. Chorioretinitis can be caused by infection with cytomegalovirus (CMV), Varicella-Zoster (HZV), dengue fever, West Nile virus or lymphocytic choriomeningitis virus (LCMV).

In particular, the viral diseases of the eye are caused by a virus from the Herpesviridae family of viruses, or by an adenovirus selected from the group consisting of 3, 4, 7, 8, 19, 29, and 37.

Herpesviridae are viruses having a double-stranded, linear DNA genome which are classified in Baltimore class I. Viruses from the Herpesviridae family causing viral diseases of the eye include, but are not limited to, type I Herpes simplex virus, human cytomegalovirus and Herpes zoster virus, in particular Herpes zoster ophthalmicus.

Adenoviridae are double-stranded DNA viruses which are classified in Baltimore class I. A *adenovirus* types 8, 19, 29, and 37 can cause epidemic keratoconjunctivitis, and *adenovirus* types 3, 4, and 7 can cause pharyngoconjuctival fever types 8, 19, 29, and 37 can cause epidemic keratoconjunctivitis, and Adenovirus types 3, 4, and 7 can cause pharyngoconjuctival fever.

The terms "treating" and "treatment," as used herein, refer to administering to a subject having a viral infection of the eye a therapeutically effective amount of an RNase such as ranpirnase, a ranpirnase variant such as the '805 variant, Amphinase 2, or rAmphinase 2. As used herein, the term "treating" covers any treatment of a viral infection of the eye which results in a desired pharmacologic and/or physiologic effect, including arresting disease development, causing regression of the disease, limiting spread of the virus from one cell to another within an individual, limiting replication of a virus in an individual, limiting entry of a virus into the cell of an individual and reducing the number of viruses in an individual or a tissue of this individual.

The term "therapeutically effective amount" is used interchangeably herein with the term "therapeutically effective dose" and refers to an amount of an RNase that results in an improvement or remediation of the symptoms of a disease or condition to be treated. A therapeutically effective amount of an RNase such as ranpirnase, '805 variant, Amphinase 2, or rAmphinase 2, in one embodiment, delays or minimizes the onset of, or hastens or increases recovery of a subject from, a viral infection of the eye in a subject. In one embodiment, the RNase reduces the viral titer in the eye of the infected subject. In another embodiment, the RNase prevents the viral titer in the eye of the infected subject from increasing. In one embodiment, a therapeutically effective amount of an RNase provides a therapeutic benefit in the treatment or management of a viral infection of the eye. In one embodiment, a therapeutically effective amount of an RNase reduces the spread of the virus from one cell to another. A therapeutically effective amount may also prevent disease and/or reduce the severity of symptoms.

A therapeutically effective amount can be determined by the skilled person as a matter of routine experimentation. The therapeutically effective dosage of the pharmaceutical composition can be determined readily by the skilled artisan, for example, from animal studies. In addition, human clinical studies can be performed to determine the preferred effective dose for humans by a skilled artisan. Such clinical studies are routine and well known in the art. The precise dose to be employed will also depend on the route of administration. Effective doses may be extrapolated from dose-response curves derived from *in vitro* or animal test systems. The RNase may be administered to a subject in need thereof in a single dose or in multiple doses. In one embodiment, the RNase is administered to a subject in need thereof once per day, or in multiple doses per day. In one embodiment, the RNase is administered to the subject until symptoms resolve and/or until the subject is no longer at risk of a virus infection.

In some embodiments, the administration of a therapeutically effective amount of the RNase, in particular ranpirnase, reduces the virus titer in the eye compared to a control not treated with the RNase, but infected with the virus by at least 10%, preferably by at least 15%, ore preferably by at least 20% and most preferably by at least 25%.

In some embodiments, the administration of a therapeutically effective amount of the RNase, in particular ranpirnase, leads to a reduction of the virus titer below the detection level. Determination of virus titers is for example discussed in Reischl (1996) Front Biosci. 1:e 72-7, Application of molecular biology-based methods to the diagnosis of infectious diseases.

In some embodiments, the RNase, in particular ranpirnase, may be administered within 6 hours after the first symptoms of viral infection of the eye have become apparent. In other embodiments, the RNase may be administered within 8, 10, 12, 15, 18 or 24 hours after the first symptoms of viral infection of the eye become apparent or within two, three, four or five days after the first symptoms of viral infection of the eye become apparent.

In some embodiments, multiple doses of the RNase, in particular ranpirnase, are administered. The frequency of administration of these multiple doses may vary, depending on factors such as the severity of symptoms. For example, the RNase may be administered once per week, twice per week, three times per week, four times per week, every other day, once per day, twice per day or three times a day.

The duration of the administration of the RNase, in particular ranpirnase, i.e. the period over which the RNase is administered, can vary depending on factors such as the severity of symptoms, patient response, etc. For example, the RNase can be administered over a period ranging from one day, three days, seven days, two weeks, four weeks, two months, three months, four months, five months or six months or longer.

The RNase, in particular ranpirnase or pharmaceutical composition comprising an RNase, preferably ranpirnase, is preferably administered topically to the eye, meaning that the RNase or pharmaceutical composition comprising RNase is administered directly to the eye and not to another place of the body. The topical administration may be by eye drops, a suspension, an emulsion, an ointment, a solution, a gel, liposomes, nanoparticles, microemulsions, nanoemulsions, nanosuspensions, niosomes, dendrimers and hydrogels .

The site of action of ranpirnase administered topically may be different layers of the cornea, conjunctiva, sclera, and the other tissues of the anterior segment such as the iris and ciliary body (anterior uvea).

Alternatively, the RNase, preferably ranpirnase, or pharmaceutical composition comprising an RNase, preferably ranpirnase, may be administered by the intravitreal, intracameral, subconjunctival, subtenon, retrobulbar or posterior juxtascleral route.

The pharmaceutical composition containing the RNase, preferably ranpirnase, has to be sterile to be administered to the eye.

Suitable excipients for ophthalmic pharmaceutical compositions include, but are not limited to, preservatives such as benzalkonium chloride, polyquaternium-1 (Polyquad), sodium perborate, oxychloro-complex (Purite®), chlorobutanol, benzethonium chloride, cetyl pyridinium chloride, benzyl bromide, EDTA, polyaminopropyl biguanide, phenylmercury nitrate, phenylmercury acetate, thimerosal, merthiolate, acetate and phenylmercury borate, polymyxin B sulphate, chlorhexidine, methyl and propyl parabens, phenylethyl alcohol, quaternary ammonium chloride, sodium benzoate, sodium propionate, sorbic acid and SofZia.

Further excipients in the pharmaceutical composition to be administered to the eye may be used to control the viscosity of the composition and include povidone, polyvinyl alcohol, polyvinylpyrrolidone, methylcellulose, hydroxypropyl methylcellulose, hydroxyethylcellulose and carboxymethyl cellulose.

Surfactants may be added to the pharmaceutical composition for dispersing insoluble ingredients or to aid in solubilization. Preferably, non-ionic surfactants such as polysorbates including polysorbate 80 or polysorbate 20 are used. Other suitable surfactants include polyoxyl 40 stearate and polyethylene glycol.

Usually, the pharmaceutical composition also contains an ingredient to adjust the pH of the composition and to buffer within a certain pH range. The pharmaceutical composition may have a pH between 5.0 and 7.5. A boric acid vehicle or Sorensen's modified phosphate buffer may be used as buffer.

Further, a tonicity agent to adjust the tonicity of the composition can be used. Suitable tonicity-adjusting ingredients include, but are not limited to, sodium chloride, sodium nitrate, sodium sulfate, potassium chloride, dextrose, glycerol, propylene glycol and mannitol.

The term "pharmaceutical composition" as used herein encompasses a composition suitable for administration to a subject, such as a mammal, especially a

human. In general a "pharmaceutical composition" is sterile, and free of contaminants that are capable of eliciting an undesirable response within the subject

The term "pharmaceutically acceptable carrier" as used herein includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents and the like. The use of such media and agents for pharmaceutically active substances is well known in the art. These agents are generally safe, non-toxic and neither biologically nor otherwise undesirable.

Supplementary active ingredients also can be incorporated into the pharmaceutical compositions. The RNase, in particular ranpirnase and ranpirnase variants provided herein may be administered together with other biologically active agents. Alternatively, the RNase, preferably ranpirnase, is the only biologically active agent in the pharmaceutical composition.

It is possible to determine whether an RNase is non-irritating to the eye in a Draize test using the Globally Harmonized System of Classification Evaluation Criteria and using the European Economic Community Ocular Evaluation Criteria. In the Draize test the RNase is placed in the conjunctival sac of a rabbit's eye and the eye is examined at 1, 24, 48 and 72 hours after instillation of ranpirnase. The criteria evaluated are corneal opacity, iris lesion, conjunctival redness and conjunctival edema. If the score for each of these criteria is zero, the RNase is considered non-irritating to the eye. Further information on the evaluation can be taken from Figures 1 to 4.

As stated above, before the present invention, no person of ordinary skill in the art would administer to the eye ranpirnase or any of the other three above-identified proteinaceous enzymatically active ribonucleases. However, such administration of ranpirnase has been modeled using the Draize test and the results of this experiment demonstrate that ranpirnase is non-irritating as defined by two accepted standards.

Example

A 0.1% mL solution made up of 0.1% ranpirnase in a proprietary aqueous solution used as a vehicle was used as a test article. Three rabbits were used; each

was a male New Zealand White rabbit that was approximately 16 weeks old at the time of the experiment and that weighed 3.3 to 3.4 kg.

After administration of two drops of Tetracaine pre-anesthetic to the corneal surface of both eyes of each rabbit, the test article was placed in the conjunctival sac of the right eye of each rabbit by gently pulling the lower lid away from the eyeball; the lids were gently held together for approximately one second to limit the loss of the test material. The left eye of each rabbit remained untreated and served as the control. The eyes of the animals were examined at 1 (± 15 minutes), 24, 48, and 72 hours (± 1 hour) after installation of the test article. The grades of ocular reaction according to Draize (Fig. 1) were manually recorded at each examination (Figs. 2 and 3). As can be seen in Fig. 2, there was an ocular reaction in each animal one hour post-instillation of the test article but in every instance that reaction was completely resolved by 24 hours and thereafter.

To determine the degree of irritation caused by the test article using the European Economic Community Ocular Evaluation Criteria (Fig. 4), the total ocular irritation scores for the examinations at 24, 48, and 72 hours were individually added for corneal opacity, iris lesion, conjunctival redness, and conjunctival edema and the mean scores for these scoring parameters were compared to the European Economic Community Ocular Evaluation Criteria. Because all these scores (and therefore the calculated mean scores) were zero, the test subject was considered to be non-irritating as defined by the European Economic Community Ocular Evaluation Criteria.

To determine the degree of irritation caused by the test article using the Globally Harmonized System of Classification Evaluation Criteria, the 24-, 48-, and 72-hour scores were added separately for each animal and each total divided by 3 (three time points) to yield the individual mean scores for each animal. Because all these scores (and therefore the calculated quotients) were zero, the test subject was considered to be non-irritating as defined by the Globally Harmonized System of Classification Evaluation Criteria.

Hence, these test data demonstrate a new and unexpected result: ranpirnase delivered to the eye in an aqueous solution is non-irritating as defined by the Globally Harmonized System of Classification Evaluation Criteria and by the European Economic Community Ocular Evaluation Criteria, even though ranpirnase is a protein (which would be expected to be irritating to the eye).

Although this experiment was carried out using a solution of ranpirnase in a proprietary aqueous vehicle, a person of ordinary skill in the art would consider it likely that solutions of the three above-identified proteinaceous enzymatically active ribonucleases would behave in the same way because of their similarities to ranpirnase in respect of activity and homology.

Although at least one preferred embodiment of the invention has been described above, this description is not limiting and is only exemplary. The scope of the invention is defined only by the claims, which follow:

CLAIMS

1. Use of a ribonuclease that is a member of the ribonuclease A superfamily in the preparation of a pharmaceutical composition for the treatment of an adenoviral infection to the human eye, wherein the ribonuclease is ranpirnase.

2. Use of:

a. a ribonuclease that is a member of the ribonuclease A superfamily and that is non-irritating to the eye; and

b. a vehicle,

in the preparation of an ophthalmic composition for the treatment of an adenoviral infection of the human eye, wherein the ribonuclease is ranpirnase.

3. Use of an ophthalmic composition to the eye, the composition comprising:

a. a therapeutically effective dose of a ribonuclease that is a member of the ribonuclease A superfamily and that is non-irritating to the eye; and

b. a vehicle,

in the preparation of a medicament for the treatment of an adenoviral infection of the human eye, wherein the ribonuclease is ranpirnase.

4. The use of any one of claims 2 to 3, wherein the vehicle is an aqueous solution.

5. Use of ranpirnase in the preparation of a pharmaceutical composition for the treatment of an adenoviral infection of an eye, wherein the composition is to be administered topically.

6. The use according to claim 5, wherein the ranpirnase is a recombinant ranpirnase.

7. The use according to claim 5, wherein the ranpirnase is SEQ ID NO: 1 or SEQ ID NO: 2.

8. The use according to any one of claims 5 to 7, wherein the adenoviral infection is the cause of viral conjunctivitis, epidemic keratoconjunctivitis, or pharyngoconjuctival fever.

9. The use according to any one of claims 5 to 8, wherein the adenoviral infection is caused by an adenovirus 3, an adenovirus 4, an adenovirus 7, an adenovirus 8, an adenovirus 19, an adenovirus 29 or an adenovirus 37.

10. The use according to any one of claims 5 to 9, wherein the ranpirnase is formulated as an ophthalmic pharmaceutical composition.

11. The use according to claim 10, wherein the ophthalmic pharmaceutical composition is a solution, a suspension, a nanosuspension, an emulsion, a microemulsion, a nanoemulsion, an ointment, a gel, a hydrogel, liposomes, niosomes, nanoparticles, or dendrimers.

12. The use according to claim 10 or claim 11, wherein the ophthalmic pharmaceutical composition further comprises a pharmaceutically acceptable carrier and/or a pharmaceutically acceptable excipient.

13. The use according to any one of claims 5 to 12, wherein the ranpirnase is to be administered as eye drops.

14. The use according to any one of claims 5 to 13, wherein the eye is from a human.