(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
29 March 2007 (29.03.2007)

PCT

(10) International Publication Number
WO 2007/035621 A1

(51) International Patent Classification:
A61M 5/32 (2006.01) *A61F 9/00* (2006.01)

(21) International Application Number:
PCT/US2006/036260

(22) International Filing Date:
18 September 2006 (18.09.2006)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/717,865 16 September 2005 (16.09.2005) US

(71) Applicant *(for all designated States except US)*: (OSI) EYETECH, INC. [US/US]; 3 Times Square, 12th Floor, New York, NY 10036 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: SCYPINSKI, Stephen [US/US]; 7 Hodge Drive, Bridgewater, NJ 08807 (US). CALIAS, Perry [US/US]; 39 Swains Pond Avenue, Melrose, MA 02176 (US). EVERETT, Richard, R. [US/US]; 25 Timber Lane, Randolph, NJ 07869 (US). SHIMA, David, T. [US/GB]; 75 Lancaster Avenue, Barnet, Herts XX EN4 0ES (GB). BREEGI, Wisam [US/US]; 120 Bedford Road, Woburn, MA 01801 (US). LITMAN, Dana, L. [US/US]; 18 Maynard Street, Malden, MA 02148 (US).

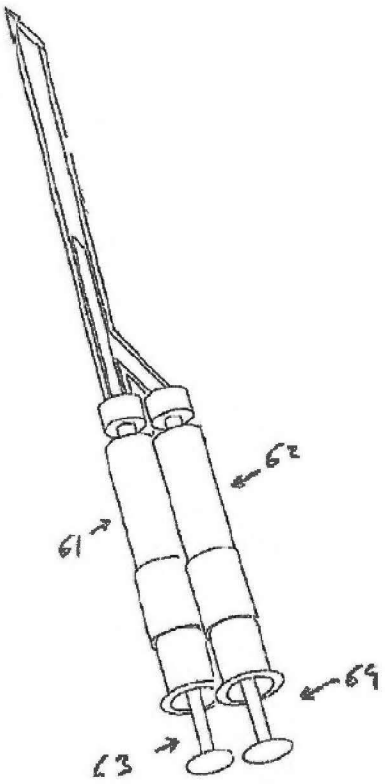
(74) Agent: RAFA, Michael, J.; (OSI) Eyetech, Inc., 3 Times Square, 12th Floor, New York, NY 10036 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH,

[Continued on next page]

(54) Title: OPHTHALMIC SYRINGE



(57) Abstract: The present invention provides a device for use in ophthalmology. In particular, the present invention provides a device for use in intravitreous administration of ocular agents. The present invention also provides methods of delivering one or more drugs to a human eye and methods for treating an ophthalmic disease, disorder, or condition.

WO 2007/035621 A1

GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

OPHTHALMIC SYRINGE

RELATED APPLICATIONS

This application claims priority to U.S. Provisional Application Serial Number 60/717,865 filed September 16, 2005, Attorney Docket No. EYE-036P, which is hereby incorporated in its entirety by reference.

FIELD OF THE INVENTION

The present invention relates to methods of administering ophthalmic medicines and devices related thereto. In particular, the invention relates to intravitreous injection using an ophthalmic syringe and needle.

BACKGROUND OF THE INVENTION

Intravitreous (IVT) injection has been used in the treatment of human ocular disease for nearly a century beginning in 1911 as means to introduce air for retinal tamponade and repair of detachment (J. Ohm, *Albrecht von Graefes Arch Ophthalmol* 1911; 79:442–450). Over the past two decades, the use of intravitreous injection has gained increasing acceptance in the therapeutic management of many intraocular diseases, particularly disorders affecting the posterior segment of the eye (Jager *et al.*, *Retina* 24:676-698, 2004). IVT injection is increasingly being incorporated into management of ocular diseases and the number of approved products for IVT injection is anticipated to grow on the basis of promising results from ongoing clinical studies. Currently formivirsen sodium (Vitravene®, Novartis AG, Basel, Switzerland), ranibizumab injection (Lucentis™, Genentech, Inc., South San Francisco, CA) and pegaptanib sodium (Macugen®, (OSI) Eyetech, Inc. NY, NY) are three medicines approved by the Food and Drug Administration as IVT injections.

Advantages of IVT injection of medicines and diagnostics include the achievement of maximum vitreous concentrations while minimizing toxicity attributed to systemic administration. While these advantages are becoming widely appreciated, the ophthalmology community turns its focus to various complications potentially associated with IVT injection. Risks of IVT injection, some vision threatening, include endophthalmitis, retinal detachment, iritis/uveitis, inflammation, intraocular hemorrhage, ocular hypertension, hypotony,

pneumatic retinopexy, and cataract (R.D. Jager *et al.*, *Retina* 24:676-698, 2004 and C.N. Ta, *Retina*, 24:699-705, 2004).

Endophthalmitis is a condition in which the tissues inside the eyeball become inflamed and is generally caused by bacterial infection. The most common sources of bacteria causing postoperative endophthalmitis are believed to be the patient's conjunctiva or eyelids. Unless treated effectively, endophthalmitis can rapidly lead to severe vision loss or blindness. The relative risks of developing postoperative endophthalmitis depend on a number of factors, including the presence of eyelid or conjunctival diseases, the patient's general health, the use of immunosuppressant medications, the type of intraocular surgery, and intraoperative complications. Of these factors, intraoperative complications, particularly breaks in the posterior capsule with vitreous loss, carry the greatest risk for the development of endophthalmitis.

Although intravitreous injection is a simple procedure with a small wound, it has been demonstrated that bacteria potentially introduced by the procedure are sufficient to induce endophthalmitis, which is likely due to the inability of the vitreous to clear the infectious microorganisms. Other equally plausible explanations for the apparent high risk of endophthalmitis after intravitreous injections may be the very limited sample size as well as publication bias. It is important, nevertheless, to minimize the risk of developing endophthalmitis by reducing or eliminating bacteria from the ocular surface at the time of the injection and to strictly adhere to aseptic technique. The use of topical antibiotics has been shown to reduce conjunctival and eyelid bacterial flora, which may in turn also decrease the risk of endophthalmitis.

Because transient increases in intra-ocular pressure (IOP) may cause mild discomfort and can be associated in rare instances with irreversible damage to retinal ganglion cells and/or retinal vascular occlusion, many investigators reported using prophylactic and/or therapeutic measures to prevent increases in IOP after IVT injection. These have included the use of aqueous paracentesis, preoperative treatment with pressure-lowering agents and digital massage or the use of a Honan IOP reducer.

Particulate contaminants present in a drug, in a syringe, or in or on materials used at the time of injection also may have the potential to induce detrimental effects when injected into the vitreous. This has been demonstrated in the case of glove lubricants, which are

highly inflammatory when injected into the posterior ocular chamber (H.S. Park, *Korean J. Ophthalmol.* 1997; 11:51-59).

Other serious complications rarely occurred after IVT injection, making it difficult, in most instances, to determine whether these were truly injection-related or simply sporadic, unrelated comorbidities.

Serious adverse events are for the most part transient and/or treatable, and the risks of serious adverse events reported after IVT injection is low. Even so, there is a need for improved devices and methods for IVT injection. The risks and benefits of IVT injection will likely carry increased weight in patient and clinician treatment as more treatment options become available.

Guidelines for IVT injection are continuing to evolve (L.P. Aiello *et al., Retina*, 24:S3-S19, 2004). For example, povidone iodine and an antibiotic are administered prior to IVT injection. Also, IVT injections are generally performed with a sterile surgical drape and lid speculum in place and a 27 or 30 gauge needle is typically used with an injection site 3.5-4.0 mm posterior to the limbus.

As new treatment modalities for macular diseases become available, the number of intravitreous injections administered is expected to increase dramatically. For example, intravitreous injection of the vascular endothelial growth factor (VEGF) inhibitor, Macugen®, has become available for the treatment of age-related macular degeneration. Also, intravitreous injections of triamcinolone acetonide are now commonly used for the treatment of macular edema.

The prevalence of endophthalmitis after intravitreous injection of anti-VEGF agents is unknown. Due to the very limited data regarding the rate of endophthalmitis after intravitreous injections, it is difficult to speculate about the true prevalence of endophthalmitis after these types of procedures. The increased use of intravitreous injections for the delivery of these agents to the retina will provide data regarding the prevalence and risk factors for post-injection endophthalmitis and in the future define a more accurate rate of endophthalmitis.

Drug delivery into the eye is challenging because the anatomy, physiology and biochemistry of the eye includes several defensive barriers that render ocular tissues

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.