IMPROVING OUTCOMES IN OPHTHALMOLOGY VIA SUSTAINED DRUG DELIVERY

In this piece, Tomas Navratil, PhD, Vice-President, Development; Benjamin Maynor, PhD, Vice-President, Research; and Benjamin Yerxa, PhD, Chief Scientific Officer, all of Envisia Therapeutics, Inc, describe the company's particle engineering technology and its application in improving the delivery of prostaglandin analogues and anti-VEGF therapy.

Despite the abundance of efficacious small and large molecular entities targeting ophthalmic diseases, the effectiveness of ocular therapies remains limited by available drug delivery methods. For topical therapies, the compliance is generally low, the bioavailability is limited by short residence times combined with low efficiency transport across the ocular surface and often there are undesirable local and systemic side effects. For intravitreal (IVT) therapies frequent, often monthly intraocular injections are required, thus exposing the patients to an excessive treatment burden and small but repeated risk of intraocular infections. By combining biodegradable polymer science with its unique PRINT® particle engineering technology, Envisia Therapeutics has developed new extended drug delivery approaches for ophthalmic drug delivery. Based on this technology, Envisia is developing novel, extended-release therapies for the treatment of glaucoma, age-related macular degeneration (AMD) and other ophthalmic diseases, with extended treatment effect ranging from weeks to months following a single dose.

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BIODEGRADABLE POLYMER SCIENCE MEETS PRINT PARTICLE ENGINEERING

To address the unmet medical need in ophthalmic drug delivery, Envisia has combined its PRINT particle engineering technology with biodegradable polymer science. The PRINT technology offers a unique ability to reproducibly fabricate particles of virtually any size, shape, chemistry, surface functionality, modulus and porosity. Additionally, PRINT has been shown previously to be broadly compatible with a wide range of biodegradable polymer chemistries and molecular entities including small molecules, nucleic acids, enzymes, and therapeutic monoclonal antibodies (see Figure 1).[1]

BIODEGRADABLE NANO- AND MICRO-PARTICLE SUSPENSIONS & IMPLANTS

The unique flexibility of PRINT has been used to develop biodegradable nano- and microparticle suspensions and biodegradable implants for extended drug delivery into the eye. The resulting PRINT-based ocular formulations are capable of targeting all major ocular tissues: the ocular surface (subconjunctival implants and topical nano- and microsuspensions); the anterior chamber (intracameral implants and subconjunctival implants); and the vitreous/retina (IVT implants and IVT microsuspensions,

Dr Tomas Navratil
Vice-President, Development

Dr Benjamin Maynor
Vice-President, Research

Dr Benjamin Yerxa
Chief Scientific Officer
T: 919 973 1440
F: 919 973 1441
E: ben.yerxa@envtx.com

Envisia Therapeutics, Inc.
P.O. Box 110065
Research Triangle Park
NC 27709
United States

www.envisiatherapeutics.com

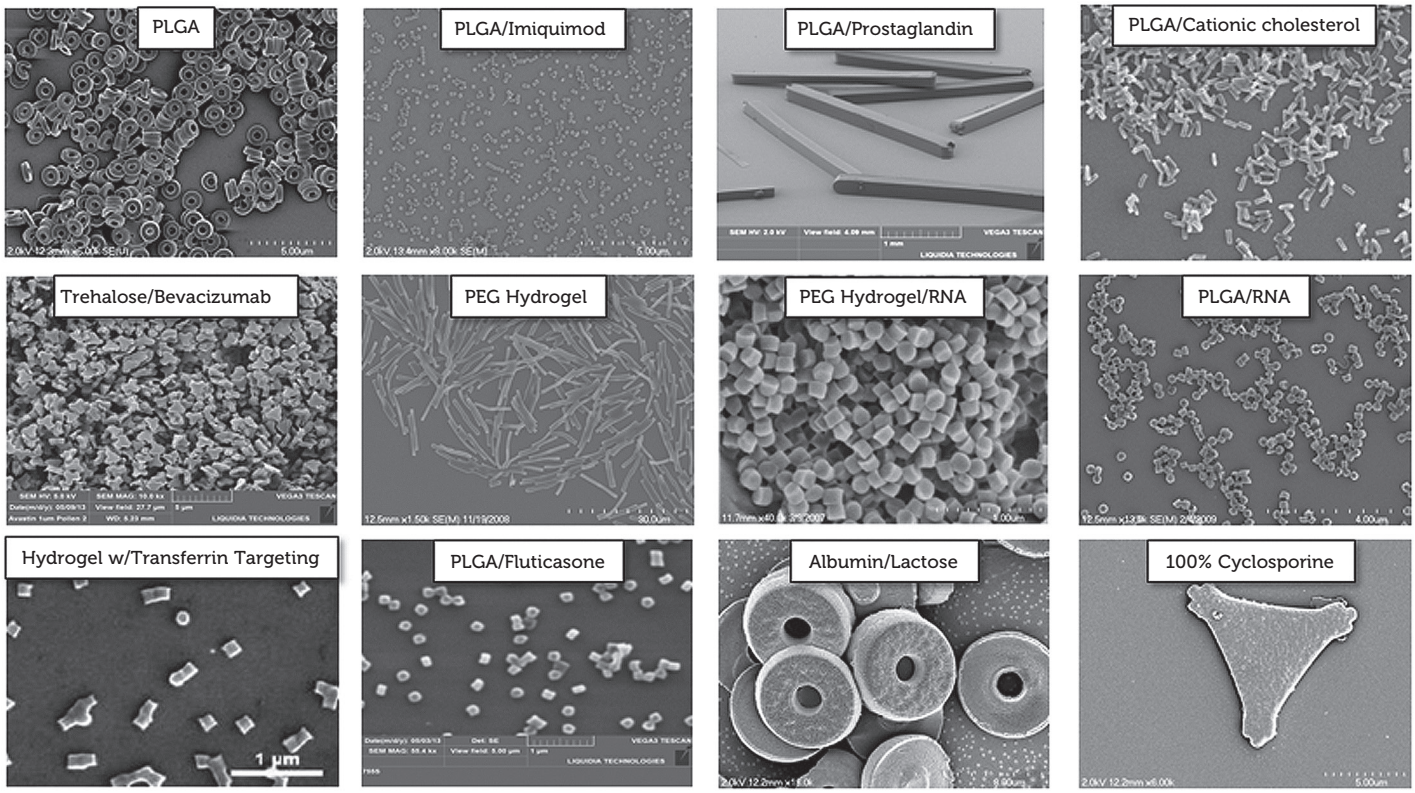

Figure 1: PRINT technology is compatible with small molecules and biologics and allows for precise control of size, shape and chemistry.

see Figure 2a). Lastly, the availability of numerous biodegradable polymer chemistries results in fully tuneable sustained rates of drug release (Figure 2b). In combination with targeted delivery into individual anatomical compartments in the eye, these tuneable features are essential to the development of future ophthalmic therapies with extended efficacy and fewer side effects.

OPPORTUNITIES FOR EXTENDED DELIVERY OF PGAS IN GLAUCOMA

Glaucoma is an optic neuropathy that results in progressive and irreversible visual field deterioration. It affects approximately 70 million patients and is the second leading cause of blindness worldwide. Prostaglandin analogues (PGAs) are the most prescribed class of topical therapies for glaucoma in the US but possess several shortcomings: low adherence; hyperaemia side effects; and fluctuation in ocular drug levels and intraocular pressure (IOP).[2,3] For example, a high percentage of patients experience hyperaemia side effects and as many as 30-60% of patients discontinue topical therapies for glaucoma within the first year of treatment.[4] Additionally, the

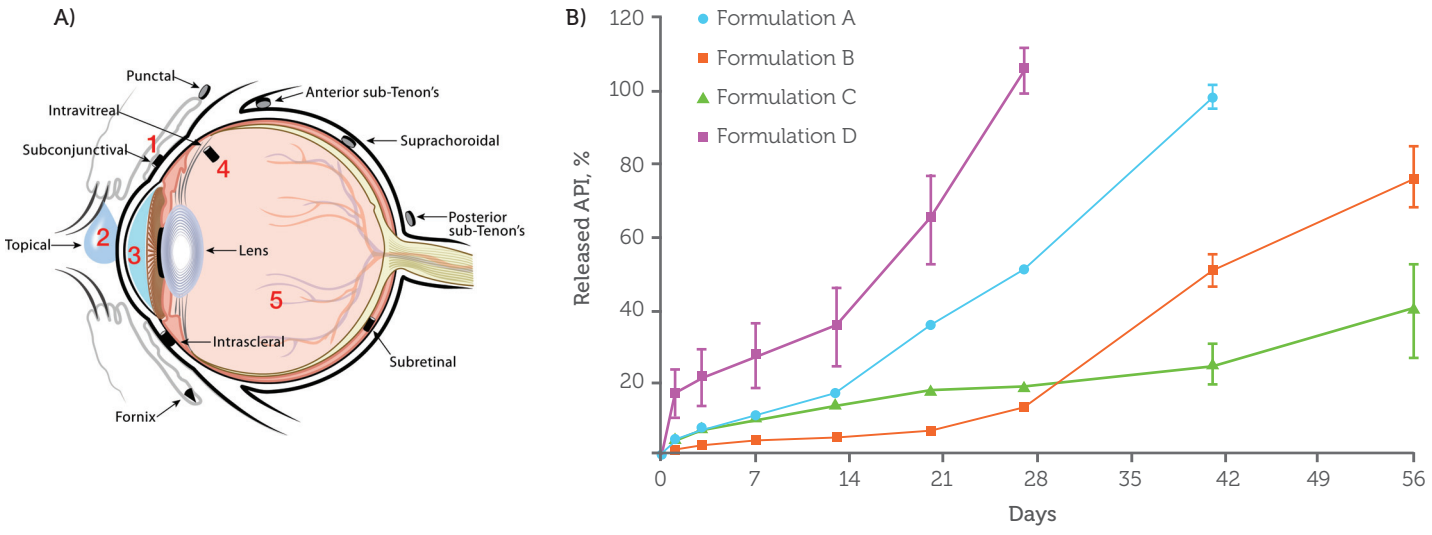

Figure 2: A) PRINT-based subconjunctival (1), intracameral (3) and intravitreal (4) implants, and topical (2) and IVT (5) Suspensions. B) Tuneable drug release from PRINT formulations.

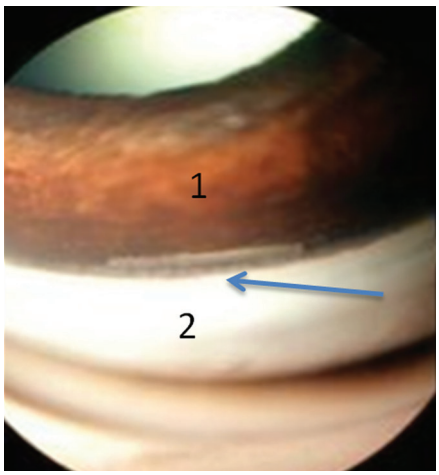

Figure 3: ENV intracameral insert in iridocorneal angle of beagle dog (1. iris; 2. cornea).

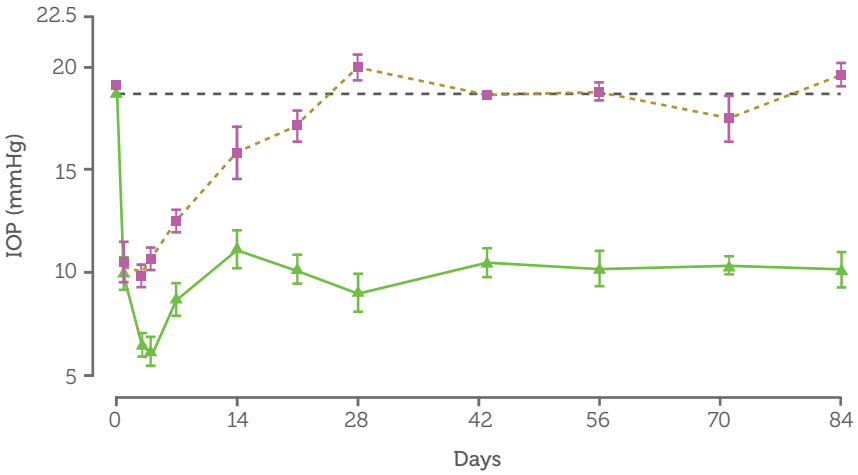

Figure 4: IOP-lowering effect of ENV55-8 – PGA extended-release formulation in normotensive beagle dogs (green: ENV55-8, purple: placebo).

"The simple in-office insertion procedure, the implied 100% compliance, and the sustained drug levels leading to lasting IOP-lowering effects address the top shortcomings of the existing topical PGA therapies"

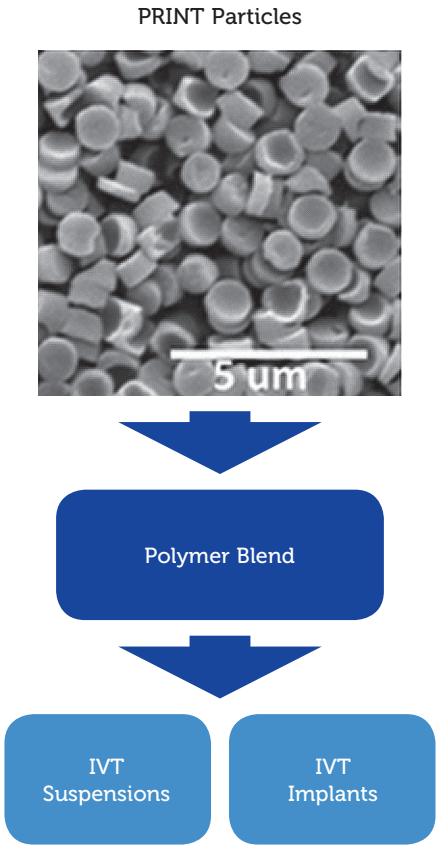

Figure 5: Envisia formulation process for extended-release IVT biologics.

daily bolus administrations of topical therapies lead to drug level peaks and troughs, which in turn may lead to IOP fluctuations and potential faster disease progression. Targeted, extended-release formulations of PGAs are being developed by Envisia to address the key shortcomings of topical PGAs.

ENV515 INTRACAMERAL EXTENDED-RELEASE PGA FOR GLAUCOMA

Envisia is developing ENV515 PGA therapy, a PRINT-based biodegradable polymer drug delivery system using an extended-release formulation of the PGA. The PRINT technology was used to fabricate ENV515 as a rod-shaped implant to fit the anatomy of the iridocorneal angle in the anterior chamber (see Figure 3), and to allow its administration via acceptably-sized needle.

Multiple formulations were evaluated in preclinical models and demonstrated robust, sustained IOP-lowering effect for periods of 3-8 months following single insertion via intracameral injection (see Figure 4 for a representative formulation). The simple in-office insertion procedure, the implied 100% compliance, and the sustained drug levels leading to lasting IOP-lowering effects address the top shortcomings of the existing topical PGA therapies. ENV515 is currently in preclinical development. Envisia plans to initiate clinical trials of ENV515 in glaucoma patients in the second half of 2014.

OPPORTUNITIES FOR EXTENDED DRUG DELIVERY OF ANTI-VEGF THERAPY FOR WET AMD

AMD is a retinopathy characterised by choroidal neovascularisation (CNV) and central retinal thickening due to vessel leakage resulting in macular oedema. These pathophysiologies occur due to increased secretion of vascular endothelial growth factor (VEGF) and lead to consequent rapid vision loss, with AMD becoming the leading cause of blindness in the elderly in the developed world.[5]

There are approximately 30 million AMD patients worldwide, with the overall financial cost of visual impairment due to AMD being assessed at US$343 billion (2010 estimates based on approximately three million blind individuals due to AMD).[6] The current standard of care is based on repeated, office-based intravitreal injection of anti-VEGF therapies comprising monoclonal antibodies (bevacizumab and ranibizumab) and VEGF receptor-trap (aflibercept). The first approved effective anti-VEGF therapy is indicated for monthly intravitreal injections.

However, to reduce the cost, patient treatment burden and risk of infection, other approaches with less frequent dosing – such as treat and extend or *pro re nata* – have been proposed and studied. The optimal schedule has currently not been determined and can differ from patient to patient. Targeted, extended-release formulations of anti-VEGF therapies would likely address the key short-

comings of the current standard of care. However, none are approved today.[5]

ENV705 EXTENDED-RELEASE ANTI-VEGF THERAPY FOR AMD

Extended-release, biodegradable implants of anti-VEGF therapies may reduce burden on patients and physicians, and improve outcomes. However, development of such therapies is a challenge due to the fragile nature of anti-VEGF biologics. The PRINT technology provides the unique ability to control size, shape and biological activity of protein particles. Envisia has developed a formulation process in which monodisperse PRINT particles are composed of excipients and anti-VEGF agents. These microparticles are then uniformly dispersed throughout various polymer blends and moulded into IVT implants or microsuspensions (see Figure 5).

The resultant IVT formulations retain the anti-VEGF activity and are tuneable for rate of and duration of drug release (Figure 6). Retention of the biological activity and the tuneable properties are essential for the development of the future extended-release anti-VEGF agents for AMD.

CONCLUSIONS AND FORECAST

Envisia Therapeutics has developed a targeted extended drug delivery technology at an intersection of biodegradable polymer science and PRINT-based particle engineering. Similarly to the PGA intracameral formulations (Figures 3 and 7B), Envisia's subconjunctival formulations are fabricated as rod-shaped implants and enable extended drug delivery to the ocular surface and into the anterior chamber (Figure 7A). Hence Envisia's nanosuspension, microsuspension, and implant based, extended-release formulations are capable of targeting the ocular surface, anterior chamber and posterior segment with both small molecules and biologics (Figures 3-7).

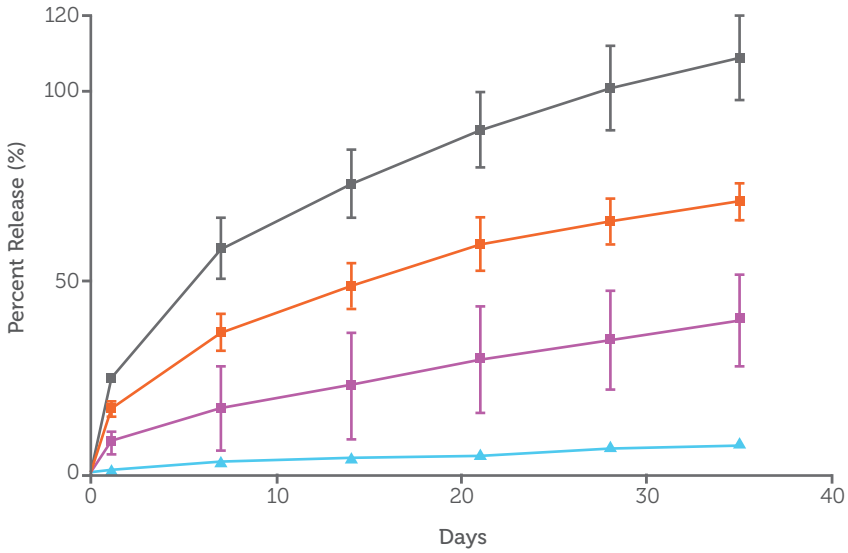

Figure 6: Tuneable rate of release for PRINT-based anti-VEGF formulations.

"Retention of the biological activity and the tuneable properties are essential for the development of the future extended-release anti-VEGF agents for AMD"

Envisia is currently developing multiple extended-release therapies for the treatment of ophthalmic diseases.

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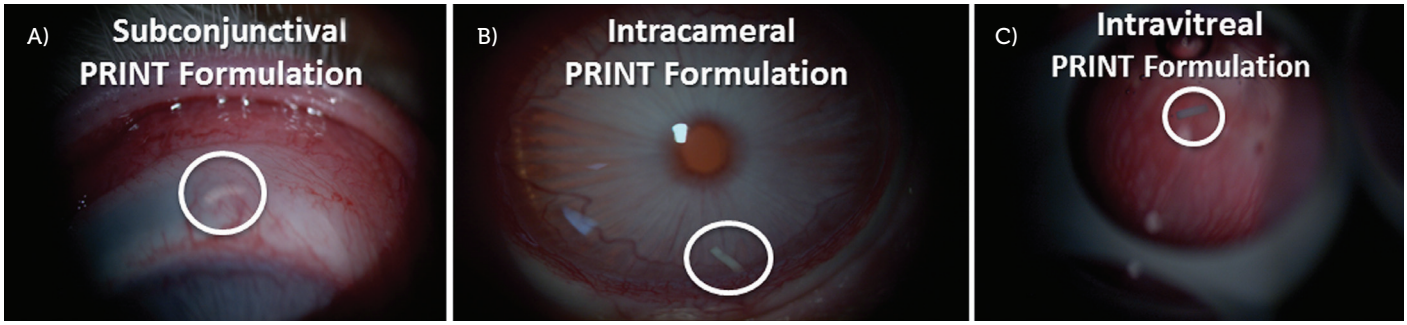


Figure 7: PRINT-based sustained-release formulations administered as subconjunctival (A), intracameral (B), and intravitreal (C) implants in New Zealand white rabbits.

envisia™ THERAPEUTICS

COMPANY PROFILE

CUTTING EDGE TECHNOLOGY, TRANSFORMATIVE OCULAR THERAPEUTICS

The Challenge

As many as 285 million people suffer from disease-related visual impairments and blindness,[1] but an estimated 80 percent of these visual impairments are actually preventable.[2] Unfortunately, the safety and effectiveness of many medical therapies for ocular disorders are limited due to poor drug uptake, non-specificity to target tissues, systemic side effects, or poor adherence to therapy. With a rapidly aging population, the unmet medical needs of patients with ocular disease are becoming even more pronounced. As a result, patients and physicians are seeking improved ocular therapeutics that can significantly enhance patient outcomes and convenience.

The Company

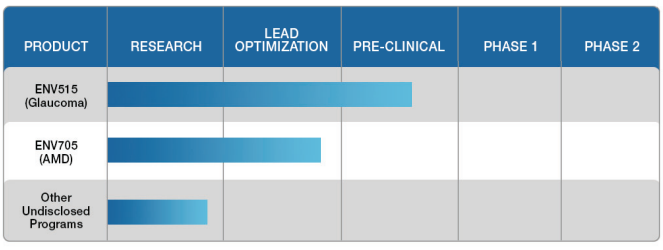
In 2013, Liquidia Technologies spun out Envisia Therapeutics, a new company committed to engineering the future of ophthalmology. At Envisia, a talented team of scientists is harnessing the unique characteristics of a revolutionary product development technology to create novel therapeutics that can address critical unmet needs in ophthalmology and transform the treatment of ocular disease.

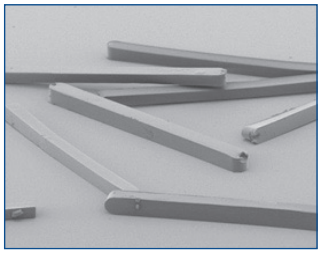
The Technology

To address these critical unmet needs, Envisia is using the proprietary PRINT® technology to rationally design and manufacture micro- and nanoparticle systems. Unlike self-assembled particle systems or harsh micronization techniques, the PRINT technology offers the unique ability to rationally design precise particles of virtually any size, shape and chemistry, including small-molecule active pharmaceutical ingredients (API), biologic APIs, nucleic acids, and polymeric drug delivery systems (e.g. extended release formulations). Also, because each particle is manufactured with precision, the PRINT particles and implants have been designed to have unparalleled lot-to-lot and dose-to-dose consistency. These particles are designed and manufactured with the goal of next-generation therapeutics that have improved delivery, safety and efficacy.

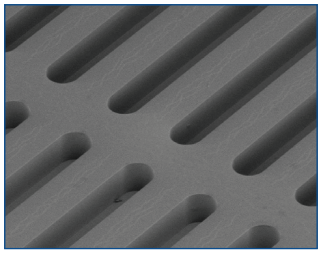
The Pipeline

Envisia's lead product, ENV515, is an undisclosed marketed prostaglandin analogue that uses a proprietary, fully biodegradable PRINT particle formulation to provide sustained intraocular pressure (IOP) reduction over many months, offering the potential to address the poor compliance that exists today and to limit glaucoma progression and vision loss. Envisia plans to initiate clinical development for ENV515 by the second half of 2014. Envisia is also developing ENV705 for wet age-related macular degeneration (AMD) and exploring how this unique technology can address other important ocular diseases.





Biodegradable PRINT particles are implantable in various compartments of the eye.



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Contact

ENVISIA THERAPEUTICS
P.O. Box 110065
Research Triangle Park, NC 27709

Phone - (919) 973-1440
Fax - (919) 973-1441
Email - info@envisiatherapeutics.com

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