

I-vation™ Sustained Drug Delivery System: Intravitreal Implant for Drug Delivery

INTRAOCULAR DRUG DELIVERY

Technologies that can provide sustained intraocular delivery of drugs for months to years will dramatically improve the treatment of chronic ocular disease. In addition to minimizing systemic drug levels and overcoming physiological barriers to drug penetration, this approach

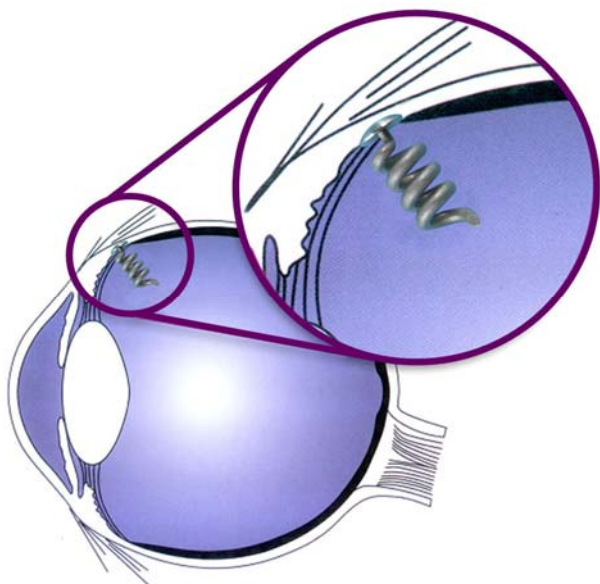


Figure 1. I-vation™ Sustained Drug Delivery System.

minimizes the dependence on patient compliance. Unlike diseases of the front of the eye, where drugs can be delivered in eye drops and other conventional ophthalmic formulations, retinal diseases require a more site-specific approach. Topical drops rarely penetrate the back of the eye and a blood-ocular barrier hinders penetration of systemically administered drugs into ocular tissue.

Despite the emergence of new drugs for retinal diseases, current standard of care requires they be administered by direct injection into the vitreous, or back of the eye. Because of the relatively short intraocular half-life of these drugs, these injections must be repeated every 4 to 6 weeks. This schedule is difficult for patients to endure and maintain, and carries an increasing risk of tissue damage and infection. With many companies developing drugs for retinal disease, the need for more optimal ocular drug delivery solutions has never been more acute.

OCULAR DRUG DELIVERY APPLICATIONS

Retinal diseases, such as Age-related Macular Degeneration (AMD) and Diabetic Macular Edema (DME), represent the leading causes of vision loss in the Western world.

Diabetic retinopathy is the leading cause of legal blindness among Americans between 20 and 74 years of age. There are an estimated 500,000 cases of macular edema in the United States, and 325,000 of these cases represent clinically significant macular edema, i.e., cases with a higher risk of vision loss. An estimated 80,000 cases of macular edema, 56,000 cases of clinically significant macular edema, and 5,000 new cases of legal blindness are reported each year as a result of diabetic retinopathy.

AMD is estimated to affect 28% of people between the ages of 65 and 75, and afflicts over 46% of people aged 75 and older. There are approximately 200,000 new cases of AMD each year in the United States, and the annual incidence is expected to grow as the population ages. Several products are currently approved for treatment of the exudative or “wet” form of this disease (approximately 10% of AMD patients have the “wet” form).



Figure 2. I-vation™ Sustained Drug Delivery System.

Sustained intraocular drug delivery may also prove to be an attractive alternative to topical eye drops for anterior diseases such as **glaucoma**. Glaucoma medications, the majority of which are delivered topically, represent a market with sales approaching \$2 billion annually. Patient compliance is a significant problem with topical administration, particularly in the elderly population.

It is recognized that fewer than 30% of patients administer drops as indicated. This lack of patient compliance can lead to the necessity for costly and invasive surgical procedures. A sustained intraocular delivery system capable of

providing medications for months at a time would represent a significant improvement in the treatment of this patient population.

THE I-VATION™ SUSTAINED DRUG DELIVERY SYSTEM

SurModics has developed the I-vation Sustained Drug Delivery System for the sustained release of drugs to the back of the eye (Figures 1 & 2). The I-vation platform offers a great deal of versatility and flexibility for formulation and pharmacokinetics control. The sustained drug delivery system leverages SurModics' proven polymer technology with a unique scaffold designed for minimally invasive implantation. The implant's small diameter enables implantation through a pars plana needlestick less than 0.5 mm in diameter. The unique helical design maximizes the surface area available for drug delivery, and ensures secure anchoring of the implant against the sclera, keeping it out of the visual field and facilitating retrieval. The thin cap is designed to reside under the conjunctival membrane of the eye (Figure 3).

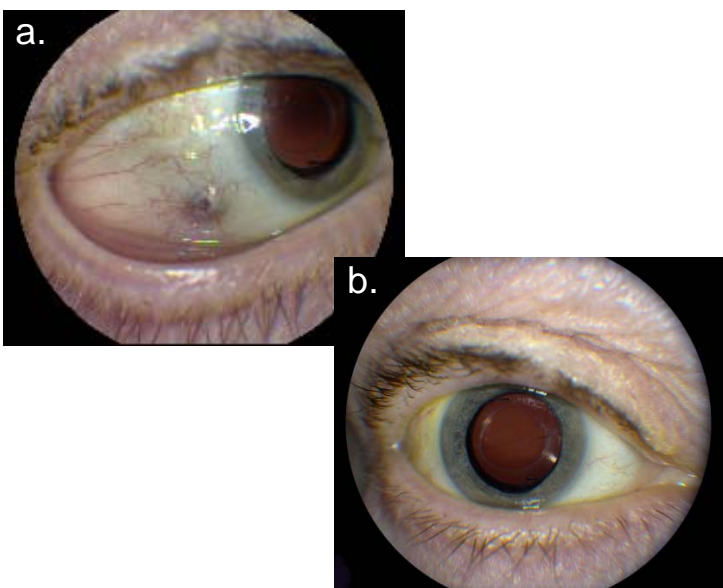


Figure 3a. Cap of I-vation TA* covered by conjunctiva (patient 7 days post-implantation). Figure 3b. Cap no longer visible when lower lid is not retracted.

The I-vation system is positioned to take advantage of SurModics' patented drug delivery technology which utilizes combinations of durable and biodegradable polymers and drug. The release of drug from these coatings is controlled by the drug loading and the composition of the polymer components, both of which influence the rate at which drug diffuses out of the coating. In addition, SurModics has a range of polymer systems which confer added flexibility to the sustained delivery system, allowing for controlled delivery of a range of therapeutic molecules from small hydrophobic drugs to larger macromolecules and proteins.

SurModics seeks to partner with pharmaceutical, biotechnology, and ophthalmology companies to further develop the I-vation platform for delivery of novel compounds for the treatment of ocular disease.

Essential Components of the I-vation Sustained Drug Delivery System

- ◆ Rigid non-ferrous metallic scaffold
- ◆ SurModics' patented polymer coating
- ◆ Active drug substance contained within the polymer coating

BRAVO™ DRUG DELIVERY POLYMER MATRIX COATING

The SurModics I-vation Sustained Drug Delivery System uses SurModics' Bravo drug delivery coating to control release of active drug. The Bravo Drug Delivery Polymer Matrix is a durable polymer matrix especially suited to the delivery of hydrophobic molecules. It can be customized to deliver drugs for durations ranging from minutes to months to well over a year. The Bravo polymer matrix is a critical component of the first-to-market Sirolimus-eluting coronary stent.

Features of the I-vation Sustained Drug Delivery System

- ◆ Sustained duration of delivery (tunable: from months to > 2 years)
- ◆ Targeted delivery for minimal systemic drug levels
- ◆ Coating platform compatible with a variety of drugs
- ◆ Removable and replaceable

I-VATION™ TA*†: AN I-VATION SUSTAINED DRUG DELIVERY SYSTEM (LICENSED TO MERCK & CO., INC. FOR FUTURE DEVELOPMENT)

Technical feasibility of the I-vation system for intraocular drug delivery has been demonstrated with I-vation TA*†, developed for sustained release of the cortico-steroid triamcinolone acetonide.

TRIAMCINOLONE

While not specifically approved for ophthalmic use, triamcinolone acetonide has a relatively long history of use in the treatment of ocular inflammation, with administration through a variety of methods, including intravitreal injection. Published reports describe the use of intravitreal triamci-

nolone in a wide range of ophthalmic disorders, including age-related macular degeneration and macular edema.

PROVEN SUSTAINED DRUG DELIVERY

As the Bravo polymer coating was optimized for delivery of triamcinolone acetone, *in vitro* elution was monitored in parallel with chemistry and manufacturing development. A broad range of elution rates was achieved (Figure 4), allowing for selection of two final dosage forms. Slower releasing formulations approximated the zero order release kinetics considered desirable to maintain consistent drug levels in the eye.

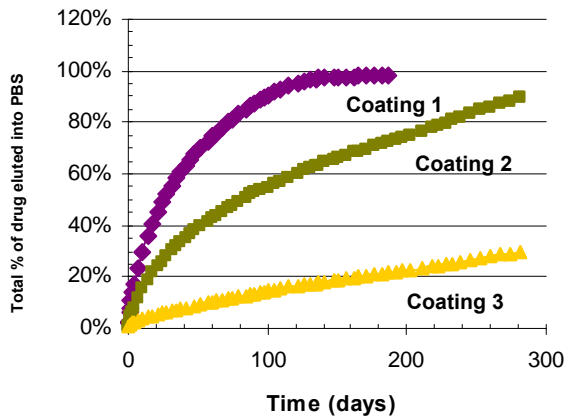


Figure 4. Example of *in vitro* drug release from drug-eluting coatings for I-vation TA^{*†}. This experiment shows that drug elution control and extended release duration can be achieved for months to years by varying the polymer matrix composition.

Elution curves generated from explanted I-vation TA^{*†} confirmed a controlled, sustained drug delivery capability *in vivo* (Figure 5). In the case of the Dose A implant, sustained delivery is predicted to last for at least 2 years.

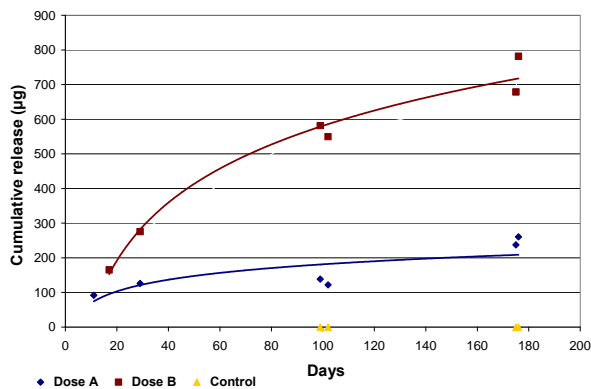


Figure 5. *In vivo* elution of triamcinolone acetone from I-vation TA^{*†}; six-month results from a pre-clinical animal model.

PRECLINICAL SAFETY AND BIOCOMPATIBILITY

Safety and biocompatibility of I-vation TA^{*†} have been studied extensively in preclinical models. In two comprehensive studies, I-vation TA^{*†} was consistently implanted in eyes in a 15 minute surgical procedure involving a sin-

gle conjunctival suture. Eyes were monitored by fundus examination, electroretinography, ocular coherence tomography, and histopathology. In a total of more than 100 eyes followed for up to 9 months post-implantation, the implant was well tolerated, with no observed retinal toxicity. In addition, very little fibrous encapsulation was observed, as demonstrated by histopathology (Figure 6).

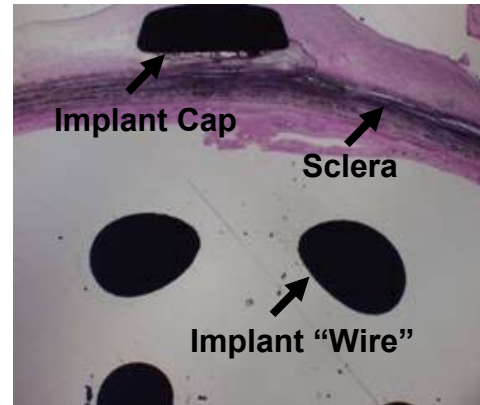


Figure 6. A 3-month post-operative resin-embedded histology section. Very little fibrous encapsulation was observed.

Removal of the implant was similarly straightforward. Following conjunctival dissection around the cap, the implant was gently rotated out of the original sclerotomy.

The remaining opening in the sclera measured approximately 0.5 mm in diameter and was either closed with a single suture or left open. The conjunctiva was closed with one or two sutures. Both techniques prevented infection and resulted in wound healing. In no case did implant removal result in retinal detachment.

Additional *in vitro* and *in vivo* biocompatibility studies for the polymer and I-vation system were performed to address requirements from ISO-10993, Biological evaluation of medical devices.

CLINICAL EXPERIENCE

SurModics is monitoring a Phase I safety study evaluating I-vation TA^{*†} in treating diabetic macular edema. Early clinical results show I-vation TA^{*†} to be safe and well tolerated. The study subjects will be followed for three years. SurModics plans to design and conduct future clinical studies that will address other chronic and/or incurable ocular disorders.

SURFACE CHARACTERIZATION

Throughout the optimization of the Bravo polymer coating for triamcinolone delivery, SurModics' extensive surface characterization capabilities were employed to evaluate surface appearance, coating thickness and uniformity. High-resolution optical light microscopy allowed visualization of coatings for a qualitative assessment of texture and uniformity.

Compared to optical microscopy, scanning electron microscopy allows both higher depth-of-field imaging around the coated surfaces of the intricate implant, and higher magnification imaging of minute surface features (Figure 7). To measure the thickness of the coating, a portion of the coating was removed, and scanning electron microscopy was used to measure the thickness difference between the coated and removed areas.

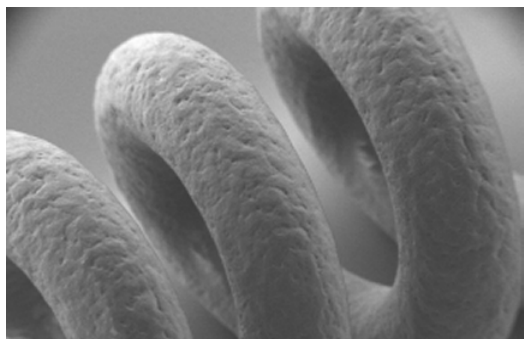


Figure 7. A scanning electron microscopic image of I-vation TA*†; note the uniformity of the coating.

Scanning confocal Raman microscopy provided a chemical “fingerprint” of the polymers and drug within the Bravo coating with a spatial resolution of 0.5 μm . The degree of mixing of the drug and polymer within the coating was imaged, and the drug was found to be finely dispersed in a small crystalline morphology throughout the depth of the polymer coating. X-ray diffraction analysis was employed to monitor polymorphic forms of the drug within the polymer coating.

REGULATORY EXPERTISE

SurModics’ regulatory expertise in early product development proved invaluable to the eventual use of the I-vation system in multi-center clinical trials. Discussions were held with the FDA regarding laboratory and preclinical work, manufacturing of clinical product, and final product testing to support a Phase I safety study. Subsequent to that meeting, SurModics filed an Investigational New Drug (IND) application to support the use of I-vation TA*† in a Phase I clinical trial for patients with DME. This application was accepted and the clinical study commenced in June of 2005.

WORKING WITH SURMODICS

It is SurModics’ mission to exceed our customers’ expectations and enhance the well-being of patients by providing the world’s foremost, innovative surface modification and drug delivery technologies and products.

In working toward this goal, SurModics provides comprehensive services throughout the product development cycle and beyond—from the initial feasibility study to

commercialization optimization, from extensive *in vitro* surface characterization and analytical support to successful technology transfer, and from manufacturing and clinical support for clinical studies to regulatory resources and ongoing customer service. The advantages of working with SurModics include:

- **Long-term commitment and support** throughout the product development cycle and beyond. Wealth of know-how and expertise produces better efficiency and productivity for speedier product development and faster time-to-market
- **Versatile drug delivery matrix technology** that can work with a variety of drugs, providing a range of release rates and durations. The Bravo polymer matrix commercialized by SurModics has been used successfully on drug-eluting stents.
- **Full service *in vitro* analytical capabilities** and QC test method development from chemical analysis for elution studies and quality control to surface and spectroscopic analysis on coating quality and drug distribution in the coating.
- **Regulatory resources and support** (FDA, CE, Japan). Device master files have been established at regulatory agencies to facilitate the approval process.
- **Clinical research resources and support** for design, implementation, and quality control of clinical studies.
- **Manufacturing process development and drug delivery matrix reagents** for commercial-scale manufacturing. SurModics also provides manufacturing support for preclinical and clinical studies and pilot-scale manufacturing services.

BRINGING INNOVATION TOGETHER

SurModics seeks to partner with pharmaceutical and biotechnology companies to further develop the I-vation sustained drug delivery system to deliver novel compounds when treating ocular disease. SurModics strives to build strong, synergistic collaborative relationships from initial contact to long-term commitment and support.

For over 20 years, SurModics has been a leading provider of surface modification technologies for medical devices and diagnostic tools. The company is a trusted and valuable product development partner bringing innovation together with its customers in the search for cutting-edge solutions to global healthcare problems.

*New Drug Limited by US Federal Law to Investigational Use Only
†I-vation TA* is Licensed by Merck & Co., Inc. for Future Development