SPECIAL EDITION 2022

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PentaVision

SPECIAL EDITION: SUPRACHOROIDAL THERAPY

Retinal PHYSICIAN

Therapeutic and Surgical Treatment of the Posterior Segment®

Suprachoroidal Drug Delivery Technology

THOMAS A. CIULLA, MD, MBA • RAFAEL V. ANDINO, MSBE, MBA • SHELLEY HANCOCK, MBA

Flow Mechanics of Suprachoroidal Injection

VENKATKRISH M. KASETTY, MD • LUKE G. QIN • DIEGO ESPINOSA-HEIDMANN, MD • DENNIS M. MARCUS, MD

Suprachoroidal Delivery as a Novel Avenue for Retinal Gene Therapy

TYLER M. EWING, MS • HANNAH KHAN, MPH • ARSHAD M. KHANANI, MD, MA

Light-activated Suprachoroidal Therapy for the First-line Treatment of Indeterminate Lesions and Small Choroidal Melanoma

BUSE GUNERI BESER, MD, FEBO, FICO • HAKAN DEMIRCI, MD

New Developments in Suprachoroidal and Subretinal Drug Delivery Technology

DAVID XU, MD • M. ALI KHAN, MD • ALLEN C. HO, MD

Suprachoroidal Drug Delivery in the Treatment of Noninfectious Uveitis

TOLULOPE FASHINA, MD, MPH • STEVEN YEH, MD

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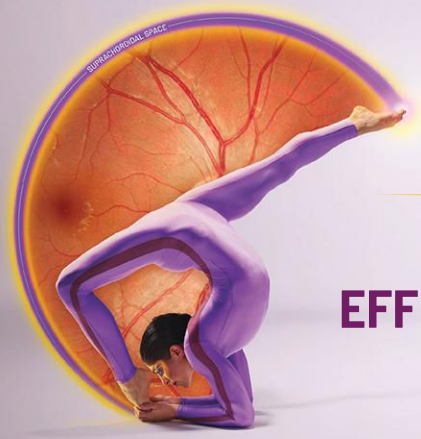

XIPERE®
(triamcinolone acetonide
injectable suspension) 40 mg/mL

IN THE MANAGEMENT OF UVEITIC MACULAR EDEMA

XIPERE® DEMONSTRATED PROVEN EFFICACY THROUGH INNOVATIVE DRUG DELIVERY VIA THE SUPRACHOROIDAL SPACE[1-5]

SIGNIFICANT AND SUSTAINED BCVA IMPROVEMENTS[1-3*]

Improvement of ≥15 ETDRS letters from baseline at Week 24 in 47% of XIPERE® patients compared with 16% in the control group (n=96 and n=64, respectively; *P*<0.01) in the pivotal trial[2]

XIPERE DELIVERED DURABILITY[3†]

344 days was the median time to rescue for patients treated with XIPERE (n=28) in an observational extension study

Additionally, 50% of patients treated with XIPERE completed the study by reaching the Week 48 visit without rescue medication

PROVEN SAFETY PROFILE

Assessed in 3 clinical studies: PEACHTREE, MAGNOLIA, and AZALEA[2,3,6]

SCAN TO DISCOVER MORE DATA AT
XIPERE.COM

J-CODE (J3299) NOW AVAILABLE FOR XIPERE®
EFFECTIVE JULY 1, 2022

*Phase 3 Study Design: 6-month, randomized, multicenter, double-masked, sham-controlled study in patients with macular edema associated with anterior-, intermediate-, posterior-, or pan-uveitis. After a 2-week screening period, eligible patients returned to the clinic for the baseline visit (Day 0) when they were randomly assigned in a 3:2 ratio to treatment or control. The control group underwent a sham procedure to maintain masking. Patients were treated at baseline and week 12. The primary efficacy endpoint was the proportion of patients in whom best corrected visual acuity (BCVA) had improved by ≥ 15 letters from baseline after 24 weeks of follow-up.[2]

†24-Week Extension Study Design: Multicenter, non-interventional, 6-month extension study for patients who successfully completed the Phase 3 study without requiring rescue treatment. The final visit of the Phase 3 study was the crossover visit (Day 0) of this study with follow-up visits conducted every 6 weeks.[3]

Indication

XIPERE® (triamcinolone acetonide injectable suspension) for suprachoroidal use is a corticosteroid indicated for the treatment of macular edema associated with uveitis.

Important Safety Information

Patients should be monitored following injection for elevated intraocular pressure. See Dosage and Administration instructions in full Prescribing Information.

- XIPERE is contraindicated in patients with **active or suspected ocular or periocular infections** including most viral diseases of the cornea and conjunctiva, including active epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, varicella, mycobacterial infections, and fungal diseases.
- XIPERE is contraindicated in patients with known **hypersensitivity to triamcinolone acetonide** or any other components of this product.
- Use of corticosteroids may produce cataracts, increased intraocular pressure, and glaucoma. Use of corticosteroids may enhance the establishment of secondary ocular infections due to bacteria, fungi, or viruses, and should be used cautiously in patients with a history of ocular herpes simplex.
- Hypothalamic-pituitary-adrenal (HPA) axis suppression, Cushing's syndrome, and hyperglycemia can occur following administration of a corticosteroid. Monitor patients for these conditions with chronic use.
- In controlled studies, the most common ocular adverse reactions were increased ocular pressure, non-acute (14%), eye pain, non-acute (12%), cataract (7%), increased intraocular pressure, acute (6%), vitreous detachment (5%), injection site pain (4%), conjunctival hemorrhage (4%), visual acuity reduced (4%), dry eye (3%), eye pain, acute (3%), photophobia (3%), and vitreous floaters (3%), and in 2% of patients: uveitis, conjunctival hyperaemia, punctate keratitis, conjunctival oedema, meibomianitis, anterior capsule contraction, chalazion, eye irritation, eye pruritus, eyelid ptosis, photopsia, and vision blurred.

  The most common non-ocular adverse event was headache (5%).
- Corticosteroids should be used during pregnancy or nursing only if the potential benefit justifies the potential risk to the fetus or nursing infant.

To report SUSPECTED ADVERSE REACTIONS, contact Bausch + Lomb at 1-800-321-4576 or FDA at 1-800-FDA-1088 or visit www.fda.gov/medwatch.

Please see brief summary of full Prescribing Information on adjacent page.

References: 1. XIPERE® [prescribing information]. Alpharetta, GA: Clearside Biomedical, Inc.; 2021. **2.** Yeh S, Khurana RN, Shah M, et al. Efficacy and safety of suprachoroidal CLS-TA for macular edema secondary to noninfectious uveitis: phase 3 randomized trial. *Ophthalmology*. 2020;127(7):948-955. **3.** Khurana RN, Merrill P, Yeh S, et al. Extension study of the safety and efficacy of CLS-TA for treatment of macular oedema associated with non-infectious uveitis (MAGNOLIA). *Br J Ophthalmol*. 2021;0:0-6. **4.** Chiang B, Jung JH, Prausnitz MR. The suprachoroidal space as a route of administration to the posterior segment of the eye. *Adv Drug Deliv Rev*. 2018;126:58-66. **5.** Rai Udo J, Young SA, Thrimawithana TR, et al. The suprachoroidal pathway: a new drug delivery route to the back of the eye. *Drug Discov Today*. 2015;20(4):491-495. **6.** Henry CR, Shah M, Barakat MR, et al. Suprachoroidal CLS-TA for non-infectious uveitis: an open-label, safety trial (AZALEA) [published online ahead of print]. *Br J Ophthalmol*. 2021;0:1-5.

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BRIEF SUMMARY OF PRESCRIBING INFORMATION
This Brief Summary does not include all the information needed to use XIPERE™ safely and effectively. See full Prescribing Information for XIPERE™.

XIPERE™ (triamcinolone acetonide injectable suspension), for suprachoroidal use

Initial U.S. Approval: 1957

INDICATIONS AND USAGE

XIPERE™ (triamcinolone acetonide injectable suspension) 40 mg/mL is indicated for the treatment of macular edema associated with uveitis.

CONTRAINDICATIONS

4.1 Ocular or Periocular Infections XIPERE™ is contraindicated in patients with active or suspected ocular or periocular infections including most viral diseases of the cornea and conjunctiva, including active epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, varicella, mycobacterial infections, and fungal diseases.

4.2 Hypersensitivity XIPERE™ is contraindicated in patients with known hypersensitivity to triamcinolone acetonide or any other components of this product.

WARNINGS AND PRECAUTIONS

5.1 Potential Corticosteroid-Related Effects Use of corticosteroids may produce cataracts, increased intraocular pressure, and glaucoma. Use of corticosteroids may enhance the establishment of secondary ocular infections due to bacteria, fungi, or viruses. Corticosteroids should be used cautiously in patients with a history of ocular herpes simplex. Corticosteroids should not be used in patients with active ocular herpes simplex.

5.2 Alterations in Endocrine Function Hypothalamic-pituitary-adrenal (HPA) axis suppression, Cushing's syndrome, and hyperglycemia can occur following administration of a corticosteroid. Monitor patients for these conditions with chronic use. Corticosteroids can produce reversible HPA axis suppression with the potential for glucocorticosteroid insufficiency after withdrawal of treatment. Drug induced secondary adrenocortical insufficiency may be minimized by gradual reduction of dosage. This type of relative insufficiency may persist for months after discontinuation of therapy; therefore, in any situation of stress occurring during that period, hormone therapy should be reinstituted. Metabolic clearance of corticosteroids is decreased in hypothyroid patients and increased in hyperthyroid patients. Changes in thyroid status of the patient may necessitate adjustment in dosage.

ADVERSE REACTIONS

6.1 Clinical Trials Experience Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. XIPERE™ was studied in a multicenter, randomized, sham-controlled, double-masked study in patients with macular edema associated with uveitis. Table 1 summarizes data available from the clinical trial for XIPERE™ treated patients and control patients. The most common ocular (study eye) adverse reactions occurring in ≥ 2% of patients and nonocular adverse reactions occurring in ≥ 5% of patients are shown in Table 1.

Adverse Reaction	XIPERE™ (N = 96) n (%)	Control (N = 64) n (%)
Ocular		
Increased intraocular pressure, non-acute [a,b]	13 (14%)	9 (14%)
Eye pain, non-acute [b]	11 (12%)	0
Cataract [c]	7 (7%)	4 (6%)
Increased intraocular pressure, acute [a, d]	6 (6%)	0
Vitreous detachment	5 (5%)	1 (2%)
Injection site pain	4 (4%)	2 (3%)
Conjunctival haemorrhage	4 (4%)	2 (3%)
Visual acuity reduced	4 (4%)	1 (2%)
Dry eye	3 (3%)	1 (2%)
Eye pain, acute [d]	3 (3%)	0
Photophobia	3 (3%)	0
Vitreous floaters	3 (3%)	0
Uveitis	2 (2%)	7 (11%)
Conjunctival hyperaemia	2 (2%)	2 (3%)
Punctate keratitis	2 (2%)	1 (2%)
Conjunctival oedema	2 (2%)	0
Meibomianitis	2 (2%)	0
Anterior capsule contraction	2 (2%)	0
Chalazion	2 (2%)	0
Eye irritation	2 (2%)	0
Eye pruritus	2 (2%)	0
Eyelid ptosis	2 (2%)	0
Photopsia	2 (2%)	0
Vision blurred	2 (2%)	0
Non-ocular		
Headache	5 (5%)	2 (3%)

[a] Includes intraocular pressure increased and ocular hypertension [b] Defined as not occurring on the day of the injection procedure, or occurring on the day of the injection procedure and not resolving the same day [c] Includes cataract, cataract cortical, and cataract subcapsular [d] Defined as occurring on the day of the injection procedure and resolving the same day

USE IN SPECIAL POPULATIONS

8.1 Pregnancy Risk Summary There are no adequate and well-controlled studies with XIPERE™ in pregnant women to inform drug-associated risks. In animal reproductive studies from the published literature, topical ocular administration of corticosteroids has been shown to produce teratogenicity at clinically relevant doses. There is negligible systemic XIPERE™ exposure following suprachoroidal injection [see Clinical Pharmacology (12.3)]. Corticosteroids should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. Animal Data Animal reproduction studies using XIPERE™ have not been conducted. In animal reproductive studies from the published literature, topical ocular administration of corticosteroids to pregnant mice and rabbits during organogenesis has been shown to produce cleft palate, embryofetal death, herniated abdominal viscera, hypoplastic kidneys and craniofacial malformations.

8.2 Lactation Risk Summary It is not known whether ocular administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in human milk. Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for XIPERE™ and any potential adverse effects on the breastfed infant from XIPERE™. There are no data on the effects of XIPERE™ on milk production.

8.4 Pediatric Use Safety and effectiveness of XIPERE™ in pediatric patients have not been established.

8.5 Geriatric Use No overall differences in safety or effectiveness have been observed between elderly and younger patients following XIPERE™ administration.

NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis No information is available on the carcinogenic potential of triamcinolone acetonide.

Mutagenesis No information is available on the mutagenic potential of triamcinolone acetonide.

Fertility No information is available on the effect of triamcinolone acetonide on fertility.

Manufactured for: Clearside Biomedical, Inc.
900 North Point Parkway, Suite 200
Alpharetta, GA 30005 www.clearsidebio.com/patents

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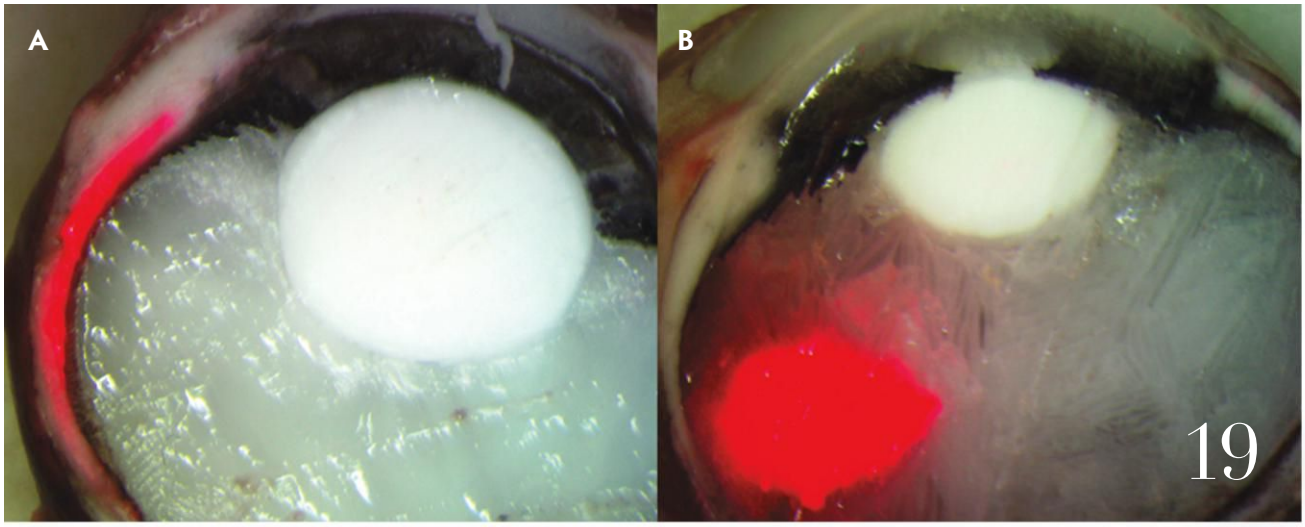

Distribution of dye injectate in ex vivo porcine eyes immediately frozen after (A) suprachoroidal injection and (B) intravitreal injection. From "Flow Mechanics of Suprachoroidal Injection," page 19. *Image courtesy of Clearside Biomedical, Inc.*

Features

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Imaging Challenge Livestream

Folloe our socials as each month, Marianeli Rodriguez, MD, from Vitreo-retinal Associates of Worcester in Boston, Massachusetts, presents interesting or challenging diagnostic images and discuss them in a livestreamed case discussion.

Watch recorded livestream videos at https://buff.ly/3vbhYUU

THE RETINA PODCAST

"Straight From the Cutter's Mouth: A Retina Podcast" is an informal space where host Jayanth Sridhar, MD, from Bascom Palmer Eye Institute in Miami invites retina specialists to discuss the latest in vitreoretinal therapies. Dr. Sridhar and his guests discuss articles from each issue of *Retinal Physician.*

Listen to past episodes at https://buff.ly/3Ah10Ze

WEB EXCLUSIVE FEATURES

Only at www.retinalphysician.com

Nonsurgical Management of Vision Degrading Myodesopsia: Part 3

Wei Gui, MD • Ronald H. Silverman, PhD • J. Sebag, MD

Vision degrading myodesopsia (VDM) refers to clinically significant vitreous floaters that merit therapeutic consideration. Article 1 of this 3-part series described etiology and diagnostics, while article 2 addressed surgical management. This third article reviews nonsurgical options.

CLINICAL TRIAL UPDATE

A complete listing of all clinical trials in AMD, DME, RVO, and uveitis, including inclusion and exclusion criteria.

retinalphysician.com/issues/2022/special-edition-2022/clinical-trial-update

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IN CASE YOU MISSED IT

Surgical Management of Vision Degrading Myodesopsia: Part 2

The diagnosis of clinically significant vitreous floaters is established on the basis of measured increases in vitreous density (by quantitative ultrasonography) and quantified degradation in contrast sensitivity function. Once the diagnosis is established and therapy is deemed appropriate, the next challenge is to cure the problem. Part 2 of this 3-part series reviews surgical intervention with vitrectomy.

Wei Gui, MD • J. Sebag, MD

retinalphysician.com/issues/2022/July-august-2022

What Is the Real Potential of the Suprachoroidal Space?

The future has arrived, and this is just the beginning.

BY JOSEPH PONZO, EXECUTIVE DIRECTOR OF MARKETING, BAUSCH + LOMB

Joe Ponzo is currently the executive director of marketing for RetinaRX products at Bausch + Lomb. He has more than 20 years of experience in varying positions within pharmaceuticals. He has an MBA in pharmaceutical management and an undergraduate degree in chemical engineering.

I wanted to personally welcome you to this special edition of *Retinal Physician*. For a long time, there has been interest in the suprachoroidal space, also known as the SCS, which is located between the sclera and the choroid and is collapsed under normal physiological conditions. Research has demonstrated that medicine may be delivered to this potential space, allowing it to reach the posterior tissues.[1]

It truly is a new era in retinal therapeutics. At Bausch + Lomb, we are excited to be able to offer Xipere, which is now available for patients with uveitic macular edema. Xipere is the first and currently the only treatment approved for delivery via the suprachoroidal space. What's most exciting is that it's certainly not the last. Here are some highlights from the clinical trials:

Significant and Sustained BCVA Improvements Seen in Clinical Trials With Xipere*[2-4]

- Improvement of ≥15 Early Treatment Diabetic Retinopathy Study letters from baseline at week 24 in 47% of Xipere patients compared with 16% in the control group (n=96 and n=64 respectively; *P*<.01).[2]

Xipere Delivers Durability[4]

- 344 days was the median time to rescue for patients treated with Xipere (n=28).
- Additionally, 50% of patients treated with Xipere completed the study by reaching the Week 48 visit without rescue medication.

Xipere has a proven safety profile as assessed in 3 trials: PEACHTREE, MAGNOLIA, and AZALEA.

In the pivotal trial, PEACHTREE, the most common adverse reactions reported by ≥10% of patients and at a rate greater than control included elevated intraocular pressure (14%) and eye pain (12%).[2,3]

In this issue, you'll find contributions on topics such as the following:

- Suprachoroidal injections and drug delivery.
- Suprachoroidal drug delivery: a new era in retinal therapeutics.
- Suprachoroidal delivery of ocular drug and gene therapy.
- Suprachoroidal drug delivery in the treatment of noninfectious uveitis: current practice and future directions.

Overall, the potential benefits of using the SCS pathway are clear[1,5]:

- **Targeted:** Circumferential and posterior spreading of the drug following injection.
- **Accessible:** Potential for high bioavailability of drug in the choroid, retinal pigment epithelium, and retina.

- **Contained:** Compartmentalization of drug away from other tissues, potentially reducing risk of certain side effects.

This special issue is packed with information to help you further explore this innovative pathway, and we hope you join your colleagues in embracing and employing the suprachoroidal space in your appropriate patients. If you're interested in learning more about Xipere, you can find more data at xipere.com or by talking to a Bausch + Lomb sales representative. **RP**

INDICATION

XIPERE® (triamcinolone acetonide injectable suspension) for suprachoroidal use is a corticosteroid indicated for the treatment of macular edema associated with uveitis.

IMPORTANT SAFETY INFORMATION

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- Corticosteroids should be used during pregnancy or nursing only if the potential benefit justifies the potential risk to the fetus or nursing infant.

To report SUSPECTED ADVERSE REACTIONS, contact Bausch + Lomb at 1-800-321-4576 or FDA at 1-800-FDA-1088 or visit www.fda.gov/medwatch.

Please see brief summary of Prescribing Information on page 29 of this publication.

***Phase 3 study design:** 6-month, randomized, multicenter, double-masked, sham-controlled study in patients with macular edema associated with anterior-, intermediate-, posterior-, or pan-uveitis. After a 2-week screening period, eligible patients returned to the clinic for the baseline visit (Day 0) when they were randomly assigned in a 3:2 ratio to treatment or control. The control group underwent a sham procedure to maintain masking. Patients were treated at baseline and week 12. The primary efficacy endpoint was the proportion of patients in whom best corrected visual acuity (BCVA) had improved by ≥ 15 letters from baseline after 24 weeks of follow-up.[1]

***24-Week Extension Study Design:** Multicenter, non-interventional, 6-month extension study for patients who successfully completed the Phase 3 study without requiring rescue treatment. The final visit of the Phase 3 study was the crossover visit (Day 0) of this study with follow-up visits conducted every 6 weeks.[3]

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1. Chiang B, Jung JH, Prausnitz MR. The suprachoroidal space as a route of administration to the posterior segment of the eye. *Adv Drug Deliv Rev.* 2018;126:58-66. doi:10.1016/j.addr.2018.03.001
2. Clearside Biomedical, Inc. XIPERE® [prescribing information]. 2021.
3. Yeh S, Khurana RN, Shah M, et al. Efficacy and safety of suprachoroidal CLS-TA for macular edema secondary to noninfectious uveitis: phase 3 randomized trial. *Ophthalmology.* 2020;127(7):948-955. doi:10.1016/j.ophtha.2020.01.006
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An Inflection Point for Retinal Therapy

Suprachoroidal administration could change the landscape of retina.

MARK BARAKAT, MD

The field of retina continues to rapidly advance and we, as retinal physicians, continue to evolve our practice to incorporate new innovations. Intravitreal injections have been the mainstay of in-office drug delivery, helping to revolutionize the treatment of exudative pathologies with the introduction of anti-VEGF agents and, more recently, with the entry of a bispecific anti-VEGF/Ang2 agent. However, the route of in-office administration has largely stayed the same with each incremental advancement over the past 2 decades. The recent approval of Xipere (Bausch + Lomb), validating suprachoroidal drug delivery and making it a clinical reality, may well be seen as an inflection point in the future: we now have an alternative route of administration, which targets posterior structures with limited anterior-segment exposure.

This special edition of *Retinal Physician*, supported by Bausch + Lomb, is intended to explore the potential benefits of the suprachoroidal route, the experience with injections into the suprachoroidal space (SCS) that brought us Xipere, and future avenues being explored.

Noninfectious uveitic macular edema is the indication that has ushered in suprachoroidal injections from trial to clinic. This issue includes a feature describing the role and potential benefits of SCS steroid delivery in this setting.

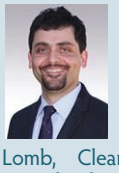
Because the injection technique and delivery site differ from traditional intravitreal injections, this issue also offers a review of the technique, as well as the safety and reliability profile of SCS injections from the collective experience across numerous trials for a variety of retinal disorders, with an overview of pipeline SCS agents. Further insights into the anatomy and biomechanics of suprachoroidal delivery via microneedle injection are also presented, as well as 2 different modalities of accessing the SCS, via microneedle vs tunneled suprachoroidal catheter.

> ... we now have an alternative route of administration.

One of the potential applications of SCS injections garnering interest is gene therapy. Because our current approach to gene therapy employs viral vectors to transduce target tissue and generate therapeutic product, a key consideration in delivering these agents is circumventing or mitigating the immune reaction and subsequent inflammation elicited by viral vectors as a class. Although recent strategies include steroid prophylaxis for intravitreal administration and delivery to the immune-privileged subretinal space via a surgical route, suprachoroidal injection is uniquely positioned as an in-office treatment with a potentially reduced inflammatory profile. The application of SCS delivery in gene therapy and the associated current trials in diabetic retinopathy and exudative AMD are reviewed in this issue.

Another condition that might potentially benefit from a suprachoroidal approach is the treatment of melanoma. While radiation is an effective treatment, it also comes with many negative sequelae. A feature in this issue addresses light-activated suprachoroidal therapy for the first line treatment of indeterminate lesions and small choroidal melanoma, reviewing the mechanism of action and suprachoroidal delivery of infrared dye-conjugated virus-like drug conjugates, and their potential to treat choroidal melanoma with a reduced side-effect profile.

Together, these articles aim to familiarize retinal physicians with suprachoroidal drug delivery. We hope you find them to be informative and beneficial to your practice. **RP**



Mark Barakat, MD, is a retina specialist and the director of research at Retinal Consultants of Arizona in Phoenix, Arizona. Dr. Barakat reports consultancy to Bausch + Lomb, Clearside Biomedical, Adverum Biotechnologies, Regenxbio, Genentech, Novartis, and Regeneron. Reach him at mark.barakat@gmail.com.

Retinal PHYSICIAN

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Peter K. Kaiser, MD

A Journey to the Suprachoroidal Space

Daniel White and I had worked together on multiple projects and at different companies. Thus, I was excited when Dan called me and asked to meet at the American Academy of Ophthalmology meeting in 2010. I met with him in a small hallway off the convention center floor along with some members of a research team from Georgia Tech. They showed me a hollow, micron-scale needle that they had developed to inject drugs into the suprachoroidal space (SCS), explaining that this was going to replace intravitreal injections.

I was intrigued but skeptical. I was sure this would be one of the most painful things we could do to a patient. After all, a suprachoroidal hemorrhage is one of our most feared complications during surgery, and injecting with this needle would surely cause many. Moreover, how could you monetize a needle? This was like being FedEx: you can deliver stuff, but the stuff in the box was where the money was.

Dan was not deterred and soon founded Clearside Biomedical with $4 million in Series A capital around this innovative delivery device. In a brilliant move, the device was paired with triamcinolone, a low solubility steroid, that could be delivered through the needle into the SCS. We tested the needle in animal eyes and then human donor eyes. The procedure seemed very straightforward, but would it work? We designed the first human studies, and I asked to see videos — with sound — of the first treatments. I was curious if my misgivings would be true. Would the patients scream in pain? Would there be an immediate suprachoroidal hemorrhage?

It turned out that all my worries were for naught. The patients tolerated the procedure well and, more importantly, steroids in the SCS worked: Xipere is now FDA approved.

It is hard to believe that this entire issue is based on that little needle I saw in a conference center back hallway. Therapies that were not even dreamed of at that meeting are now being delivered through the needle, including gene therapy and tyrosine kinase inhibitors. I asked a leading retina expert in SCS technology to be the guest editor for this issue. Dr. Mark Barakat has extensive experience with the device in clinical trials, and he has developed a great issue. We hope you enjoy it. **RP**

SUBSPECIALTY NEWS

BY ROCHELLE NATALONI, CONTRIBUTING WRITER

Research and industry news in retina

Oxurion Presents THR-149 and THR-687 Clinical Trial Data

■ Oxurion released data on its KALAHARI (THR-149) and INTEGRAL (THR-687) diabetic macular edema (DME) studies at the Macula Society meeting in Berlin, during presentations made by Shree K. Kurup, MD, of University Hospitals in Cleveland, Ohio, and Francesco Bandello, professor and chairman of the department of ophthalmology, VitaSalute, Milan, Italy, respectively.

Dr. Kurup's presentation on part A of the phase 2 study of THR-149 (KALAHARI), revealed that of the 3 intravitreal injections of THR-149 evaluated (0.01 mg, 0.04 mg, and 0.13 mg), in the high-dose group, a mean BCVA gain of 6.1 letters was seen at month 3, with gains observed up to month 6, as well as central subfield thickness stabilization over the 6-month study period compared to baseline, with no need for rescue treatment. Post hoc analysis, excluding 2 subjects with abnormalities on OCT, showed a mean gain in BCVA of 9.3 letters at month 3, which was maintained up to month 6.

Dr. Bandello reported on THR-687: the first part of the 2-part phase 2 INTEGRAL trial showed THR-687 to be safe and well tolerated with no serious adverse events and none of the patients requiring rescue medication through month 3. However, there was insufficient evidence of efficacy on the key endpoints — BCVA and central subfield thickness. As a result, Oxurion has decided not to advance THR-687 to part B of the INTEGRAL trial.

Researchers Identify Possible Link Between COVID Vaccine and Uveitis

■ The BNT162b2 mRNA COVID-19 vaccine might be associated with increased risk of noninfectious uveitis (NIU), according to a retrospective population-based study published in *Ophthalmology*. The study, which was performed by researchers affiliated with the department of ophthalmology at Lady Davis Carmel Medical Center in Haifa, Israel, analyzed data from 2,602,557 people who received 2 doses of the vaccine. A previous diagnosis of NIU was documented for 18,236 of those who received the first dose and 17,250 who received the second dose. Among patients with a history of uveitis there was an increased incidence of active NIU, in approximately 1 case per 1,000 vaccinated people. More than 90% of cases were anterior uveitis and treated topically.

The study suggests that the small estimated attributable risks suggest that the impact on public health is relatively minor. However, the authors state that ophthalmologists should be aware of this potential increased risk of relapse, and patients should be advised of the symptoms of active uveitis — particularly during the first 14 days following each dose.

The authors concluded, "While our results suggest an increased risk of uveitis among certain patient populations … the impact of this additional morbidity is outweighed by the reduced systemic COVID-19 morbidity achieved through vaccination."

Apellis Submits NDA to FDA for Intravitreal Pegcetacoplan

■ Apellis Pharmaceuticals submitted a New Drug Application (NDA) to the FDA for intravitreal pegcetacoplan, a targeted C3 therapy for the treatment of geographic atrophy (GA) secondary to age-related macular degeneration (AMD). Pegcetacoplan was granted Fast Track designation by the FDA, and the Agency's decision on the NDA request is expected in August 2022.

The NDA submission is based on results from the phase 3 DERBY and OAKS studies at 12 and 18 months and the phase 2 FILLY study at 12 months. In the studies, treatment with both monthly and every-other-month pegcetacoplan resulted in a clinically meaningful reduction of GA lesion growth across a broad, heterogenous population of more than 1,500 patients. Pegcetacoplan demonstrated a favorable safety profile in all 3 studies. "We are now one step closer to our goal of bringing the first GA treatment to patients living with this relentless and irreversible disease," said Jeffrey Eisele, PhD, chief development officer at Apellis, in a news release.

NIH Study Confirms Benefit of AREDS2 Formula for AMD

■ The Age-Related Eye Disease Studies — AREDS and AREDS2 — established that dietary supplements can slow progression of AMD. In a new report, scientists analyzed 10 years of AREDS2 data and showed that the AREDS2 formula, which substituted antioxidants lutein and zeaxanthin for beta-carotene, not only reduces risk of lung cancer due to beta-carotene but also is more effective at reducing risk of AMD progression, compared to the original formula. A report on the study, funded by the National Institutes of Health, was published in *JAMA Ophthalmology*.

The original AREDS study showed that a dietary supplement formulation (500 mg vitamin C, 400 international units vitamin E, 2 mg copper, 80 mg zinc, and 15 mg beta-carotene) could significantly slow the progression of AMD; however, 2 concurrent studies also revealed that people who smoked and took beta-carotene had a significantly higher risk of lung cancer than expected. "This 10-year data confirms that not

only is the new [beta-carotene-free] formula safer, it's actually better at slowing AMD progression," said Emily Chew, MD, director of the division of epidemiology and clinical application at the National Eye Institute (NEI) and lead author of the study report, in a news release.

FDA Approves Beovu for the Treatment of DME

■ Novartis announced that the FDA has approved Beovu (brolucizumab-dbll) 6 mg for the treatment of DME. The approval was based on year 1 data from the phase 3 randomized, double-masked KESTREL and KITE studies, which met their primary endpoint of noninferiority in change in BCVA from baseline vs aflibercept at year 1.

In aggregate, a numerically lower proportion of patient eyes treated with Beovu had intraretinal fluid, subretinal fluid, or both at week 52 vs eyes treated with aflibercept: in KESTREL 60.3% in the Beovu arm vs 73.3% in the aflibercept arm; in KITE 54.2% in the Beovu arm vs 72.9% in the aflibercept arm. Through year 1, half of Beovu patients (55% in KESTREL and 50% in KITE) remained on a 12-week dosing interval following the loading phase. During this time, by week 52, patients received a median of 7 Beovu injections. Patients treated with Beovu demonstrated a significant reduction from baseline in central subfield thickness starting at week 4 and continuing to week 52.

"KESTREL and KITE were the first pivotal trials to assess an anti-VEGF on 6-week dosing intervals in the loading phase, suggesting Beovu may offer fewer injections from the start of treatment through year one. We look forward to offering a new treatment option to help address the unmet needs of patients with DME," said Jill Hopkins, senior vice president and global development unit head of ophthalmology for Novartis, in a news release.

Development of Platform for Early Detection of Vision Loss Proceeds

■ Retina Technologies, Inc. (RetTech) announced that it is advancing the development of Ocuvue, a digital, modular vision screening platform that can be used remotely or integrated into any clinic. The platform allows for patients to get comprehensive vision screening exams and retinal images in 15 minutes and eliminates the need to move between multiple machines and testing rooms.

RetTech was founded by a team of medical students from the Icahn School of Medicine at Mount Sinai in New York, New York. Now RetTech is working closely with the New York Eye and Ear Infirmary (NYEE), part of the Mount Sinai Health System, to advance the development of Ocuvue. "I think the ability to get regular vision screening for early detection would be a big win-win for both doctors and patients," said James C. Tsai, MD, MBA, president of NYEE and chair of the department of ophthalmology at Mount Sinai, in a news release.

Eyenuk's Eyeart Algorithm Earns Kudos From UK Screening Committee

■ Eyenuk, Inc's Eyeart v2.1 algorithm for autonomous diabetic retinopathy screening has been confirmed as safe and cost-effective for use in level 1 grading or as a filter prior to manual grading, and it has been identified as the only diabetic eye screening AI technology ready for live clinical implementation in the United Kingdom, according to a report developed by the UK National Screening Committee. The Eyeart system provides diabetic retinopathy (DR) detection in a single office visit during a diabetic patient's regular exam. Once the patient's fundus images have been captured and submitted to the Eyeart AI system, the DR detection results are available in a PDF report in less than 30 seconds. The Eyeart system is planned for use as part of a project that will use AI to address racial and ethical health inequalities, led by the Moorfields Eye Hospital NHS Foundation Trust in London, England.

Medical Student Ocular Cancer Fellowship Established

■ Research to Prevent Blindness (RPB) and Castle Biosciences have announced the establishment of the RPB/Castle Biosciences Medical Student Eye Research Fellowship in Ocular Cancer, which will award 1 fellowship to a medical student focusing on a research project related to ocular cancer. The fellowship, which must take place prior to the student's third or fourth year of medical school, will be funded for 1 year with a $30,000 grant that will provide financial support in furtherance of the recipient's ocular cancer research activities.

"While the types of cancers that our diagnostic tests address have expanded over the years, our commitment to patients, research, and innovation has remained the same, which is why we are proud to partner with RPB to offer this grant to a deserving student interested in making a difference in the field of ocular cancer," said Derek Maetzold, president and chief executive officer of Castle Biosciences, in a news release.

Luxa Bio Doses First Participant in Phase 1/2a Dry AMD Trial

■ Luxa Biotechnology announced that the first participant has been treated in its phase 1/2a clinical trial of RPESC-RPE-4W for dry AMD, being conducted at the University of Michigan Kellogg Eye Center. The cell product being used in the clinical trial is a progenitor stage RPESC-RPE cell obtained after 4 weeks of differentiation. The

RPESC-RPE-4W progenitor stage cell has shown increased engraftment and vision rescue compared to more mature RPE cell products.

Laboratory studies of RPESC-derived RPE cells demonstrated they could perform the critical repertoire of cell functions carried out by normal RPE cells, including trophic factor release and phagocytosis. Rajesh C. Rao, MD, the trial's principal investigator, has transplanted 50,000 RPESC-RPE-4W cells under the macula of a study participant with advanced dry AMD. The phase 1/2a study will enroll up to 18 participants to assess the safety, tolerability, feasibility, and preliminary efficacy of subretinal RPESC-RPE-4W in a dose escalation, open-label study. The trial is cosponsored by the NEI of the NIH under a Regenerative Medicine Innovation Project cooperative agreement.

Study Demonstrates Effectiveness of Uplizna for Patients With NMOSD

■ Horizon Therapeutics announced data from its phase 3 pivotal trial of Uplizna in patients with neuromyelitis optica spectrum disorder (NMOSD) who have genetic variations. The data demonstrate the treatment's effectiveness among patients with different genetic makeups, including those with certain variations associated with reduced response to conventional monoclonal antibody (mAb) therapies.

Treatment for NMOSD includes the use of mAbs that bind to and deplete the B cells that drive disease activity. Increasingly, therapeutic research has shown that genetic variations in the immune system can affect the efficacy of these mAb therapies. The phase 3 study found no significant differences in disease attacks or disability regardless of *FCGR3A* genotype. "These data illustrate how mechanistic precision in treatment design can help patients gain benefit from their regimen regardless of the genetic make-up of their immune systems," Bruce Cree, MD, PhD, MAS, study author and professor of clinical neurology at the University of California San Francisco Weill Institute for Neurosciences, said in a news release.

Benefit of Corticosteroid Prior to Iluvien Confirmed by PALADIN

■ The phase 4 PALADIN study confirmed the benefit of using a course of corticosteroid prior to Iluvien to reduce the risk of intraocular pressure (IOP) spikes, according to Alimera Sciences. These results were presented at the annual ARVO meeting, by Christopher Fuller, MD, of Texas Retina Associates.

The 3-year PALADIN study evaluated the long-term safety and efficacy of Iluvien, a 0.19-mg fluocinolone acetonide (FAc) intravitreal implant, in patients with DME. The study enrolled 202 eyes in 159 patients with DME who had previously been treated with a corticosteroid and had not experienced a clinically significant rise in IOP. The eyes were treated with Iluvien, and patients were followed for up to 36 months. During the 36 months, the IOP distribution was marginally affected, with more than 96% of eyes showing a mean IOP ≤25 mmHg during any study visit.

Dr. Fuller concluded, "The steroid challenge pre-FAc is highly predictive of the IOP response post-FAc and not dependent on steroid choice or number of [dexamethasone implants]. This is evident by the small change in mean IOP of the full population and that 97% of eyes had IOP ≤25 mmHg over the 36 months post-FAc. Similarly, the steroid choice had little impact on visual acuity gains at 36 months with the full population experiencing significant vision improvement by nearly a line and eyes receiving a [dexamethasone implant] challenge were able to maintain vision."

FDA Reviews Application for Lucentis Biosimilar

■ Coherus Biologics announced that the FDA has reviewed the Biologics License Application for Cimerli (ranibizumab-ranq), a Lucentis biosimilar, and the target for possible approval of the application is August 2022. The company also announced that it has discontinued development of CHS-305 (IBI-305), an Avastin biosimilar candidate, and is returning IBI-305 rights to Innovent Biologics. Last year, Coherus discontinued development of CHS-2020, an Eylea biosimilar.

"As we prepare for as many as 4 new product launches in 2022 and 2023, we continue to make strong progress transforming Coherus into an innovative immuno-oncology company supported by revenues generated by our diversified commercial portfolio of FDA-approved products," said Coherus CEO Denny Lanfear in a news release. "Following the recent late-cycle review meeting with the FDA, we are finalizing our preparations to launch Cimerli later this year, if approved, into the $7 billion anti-VEGF ophthalmology market in the US," he added.

Alimera Partner Begins Phase 3 Study of Iluvien in China

■ Alimera Sciences' partner, Ocumension Therapeutics, received approval from the National Medical Products Administration for its investigational new drug (IND) application to begin a phase 3 clinical study of Alimera's 0.19 fluocinolone acetonide intravitreal implant, Iluvien, in mainland China. The intent of the trial is to support a future NDA filing to gain marketing approval in China, with an equivalent indication to Alimera's US indication, for the treatment of DME that was previously treated with a course of corticosteroids and did not have a clinically significant rise in IOP.

"We are very excited by the progress that Ocumension is making toward generating the data needed to seek approval in China for our intravitreal implant. We look forward to the start of the trial and to the subsequent data," said Rick Eiswirth, Alimera's president and CEO, in a news release.

> [AREDS2] not only reduces risk of lung cancer due to beta-carotene but also is more effective at reducing risk of AMD progression.

Post Hoc Analysis of GATHER1 Zimura Data Presented

■ Iveric Bio announced a post hoc analysis from the GATHER1 clinical trial, which used enhanced OCT imaging to examine the effect of Zimura (avacincaptad pegol) on change in ellipsoid zone (EZ) integrity and growth of GA, and the correlation between fundus autofluorescence (FAF) and GA progression. The results showed that OCT-measured GA area strongly correlated with FAF-measured GA area, with minimal average differences in GA area between modalities. A 30% reduction was observed in OCT-measured GA growth with Zimura at 12 months, which is consistent with findings using FAF-measured GA growth in GATHER1. In addition, a 22% reduction in progressive EZ loss/attenuation at 18 months was observed with Zimura compared to sham. The data were presented at the Macula Society meeting, in Berlin, Germany, by Justis P. Ehlers, MD, from Cole Eye Institute of Cleveland Clinic. "This important study illustrates the potential for eye care providers to accurately diagnose and monitor patients who have GA with OCT alone, without additional equipment required," said Christopher Simms, chief commercial officer for Iveric Bio, in a news release.

Nacuity Series B Financing Led by Foundation Fighting Blindness

■ Nacuity Pharmaceuticals announced the closing of $16.5 million in Series B financing led by Foundation Fighting Blindness and its venture arm RD Fund. Proceeds from the financing will be used to support the advancement of Nacuity's clinical trials for NPI-001 and NPI-002 through proof of concept, as well as for general operations. Oral NPI-001 tablets are currently being evaluated in a phase 1/2 clinical trial, the SLO-RP study, in patients with retinitis pigmentosa associated with Usher syndrome. Nacuity expects to have interim results from this study in the second quarter of 2023. NPI-002, a proprietary sustained release antioxidant molecule designed to slow cataract progression delivered via intravitreal implant, is being evaluated in a phase 1/2 clinical trial that is currently enrolling patients undergoing vitrectomy in Australia. Nacuity expects to have results from this study in the second quarter of 2023, as well.

"This funding will help further our mission to develop a breakthrough treatment for retinitis pigmentosa and other serious blinding and chronic diseases caused by oxidative stress," said Halden Conner, chairman, CEO, and cofounder of Nacuity Pharmaceuticals, in a news release.

Robot-assisted Subretinal Drug Delivery Performed in Human

■ The first-in-human study using a robotic device to assist in subretinal drug delivery in patients undergoing vitreoretinal surgery for macular hemorrhage was performed at the Oxford Eye Hospital, Oxford University Hospitals NHS Foundation Trust, Oxford, United Kingdom. A dozen participants were recruited: 6 in a robot-assisted arm and 6 in a control manual surgery arm. The researchers explained in their *American Journal of Ophthalmology* report that subretinal hemorrhage was successfully displaced at 1 month postintervention, except for 1 control subject, and the median gain in visual acuity was similar in both arms.

All study subjects presented with acute loss of vision due to a subfoveal hemorrhage secondary to neovascular AMD. After standard vitrectomy, intraoperative OCT-guided subretinal injection of tissue plasminogen activator (TPA) was performed by either robot-assisted or conventional manual technique under local anesthesia. The robotic part of the procedure involved advancement of a cannula through the retina and stabilizing it during foot-controlled injection of up to 100 µL of TPA solution.

The study demonstrates the feasibility and safety of high-precision robot-assisted subretinal drug delivery, as part of the surgical management of submacular hemorrhage, simulating its potential future application in gene or cell therapy. **RP**

Suprachoroidal Drug Delivery Technology

The first FDA approval ushers in a new clinical reality.

THOMAS A. CIULLA, MD, MBA • RAFAEL V. ANDINO, MSBE, MBA • SHELLEY HANCOCK, MBA

After the 2021 approval by the US Food and Drug Administration of Xipere (Bausch + Lomb) triamcinolone acetonide injectable suspension for suprachoroidal use (CLS-TA), for the treatment of uveitic macular edema (UME), suprachoroidal (SC) drug delivery became a clinical reality. Multiple therapies are now being assessed for SC delivery in clinical trials, including a small molecule suspension of a tyrosine kinase inhibitor (TKI), a small molecule suspension of a corticosteroid, a gene therapy, and a virus-like drug conjugate. This article summarizes the key aspects of SC delivery, development of the microneedle technology, and current clinical trials **(Table 1).**

ANATOMY

Potential spaces in the body can serve as "druggable" targets, and epidural anesthesia represents one such commonly performed application of this concept. In the eye, the suprachoroidal space (SCS) is the potential space between the choroid and sclera that circumferentially extends from the scleral spur posteriorly **(Figure 1).** Potential advantages of treating via the SCS include targeted delivery to affected chorioretinal tissues for efficacy and compartmentalization away from unaffected tissues for safety and bioavailability, because these chorioretinal tissues are essentially bathed with therapy.[1,2] For small molecule suspensions, there is potential prolonged pharmacokinetics that may yield favorable durability.[1,2]

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Potential advantages of treating via the SCS include targeted delivery to affected chorioretinal tissues for efficacy and compartmentalization away from unaffected tissues.

BIOMECHANICS OF SUPRACHOROIDAL DELIVERY

After suprachoroidal injection, a natural pressure gradient between the intraocular pressure, the anterior SCS, and the posterior SCS pressure drives SC injectates posteriorly and circumferentially towards the macula, with potential to treat macular disorders.[3] Multiple factors appear to drive durability in the SCS, including particle size. Particles ranging from the size of gene therapy viral vectors to small molecule suspensions remain primarily in the suprachoroidal space and choroid for a period of months.[4] The physiologic upper limit of pore size in the fenestrated choriocapillaris is estimated between 6 nm and 12 nm, which may limit transcapillary passage of larger macromolecules and particles.[5] In addition to particle size, the relative insolubility of small molecule suspensions contributes

Table 1: Key Aspects of Suprachoroidal Delivery of Therapeutics

• Suprachoroidal (SC) drug delivery is now a clinical reality, after the first FDA-approved therapeutic into the suprachoroidal space (SCS).
• Current trials involving SC delivery include evaluation of a small molecule suspension of a tyrosine kinase inhibitor, a small molecule suspension of a corticosteroid, a gene therapy, and a virus-like drug conjugate.
• Potential advantages of SCS administration include targeted delivery to affected chorioretinal tissues for efficacy, compartmentalization away from unaffected tissues for safety, and bioavailability.
• For small-molecule suspensions delivered via the SCS, particle size and relative insolubility contribute to durability.
• After SC injection, a natural pressure gradient (intraocular pressure > anterior SCS pressure > posterior SCS pressure) drives injectates posteriorly toward the macula, with potential to treat macular disorders.
• A procedural performance study with the SCS Microinjector (Clearside Biomedical) showed that a large majority of physician-investigators did not perceive suprachoroidal injections to be meaningfully more challenging than other ocular injections, following first use of the injector.

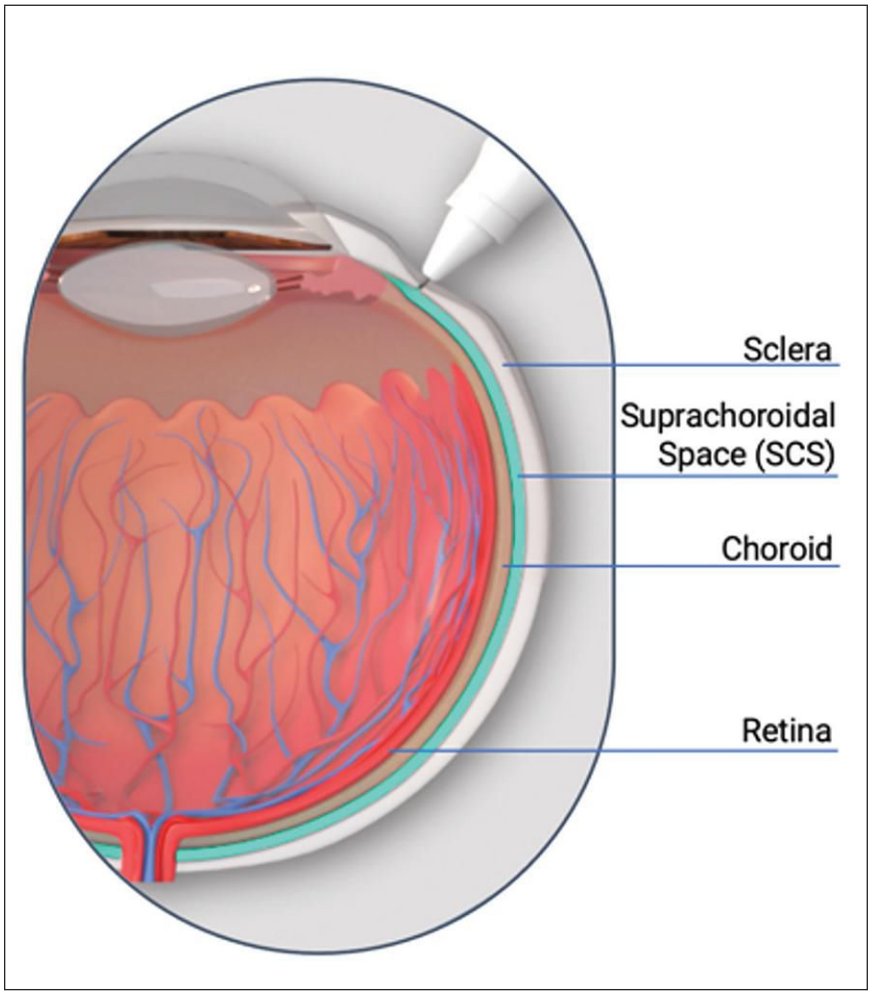

Figure 1. Illustration of injection into the suprachoroidal space via a microneedle. Suprachoroidal injection is indicated in teal, flowing posteriorly toward the macula and optic nerve.

to durability.[6-10] Preclinical studies with small molecule suspensions have shown durable high levels of drug in the targeted retina, retinal pigment epithelium, and choroid, while also limiting exposure to the anterior chamber, iris, ciliary body, and lens.[6-10] Consequently, by both maximizing drug levels in the targeted chorioretina and minimizing levels in the anterior segment of the eye, suprachoroidal injection has the potential to facilitate efficacy and safety.

RELIABLE ACCESS TO THE SUPRACHOROIDAL SPACE

The SCS Microinjector (Clearside Biomedical) precisely delivers therapies to the SCS utilizing a 900 µm or 1,100 µm length microneedle.[1,11] The 2 lengths accommodate anatomic variations in patient ocular anatomy. Suprachoroidal injection is carried out at the pars plana under local anesthesia. In clinical practice, SC injections are typically performed with the 900 µm needle by inserting the needle perpendicularly to the eye at the injection site until the needle tip penetrates through the conjunctiva and sclera to access the SCS **(Figure 2).** Pressure is then applied to the microinjector syringe plunger, followed by an initial resistance to injectate flow, because the

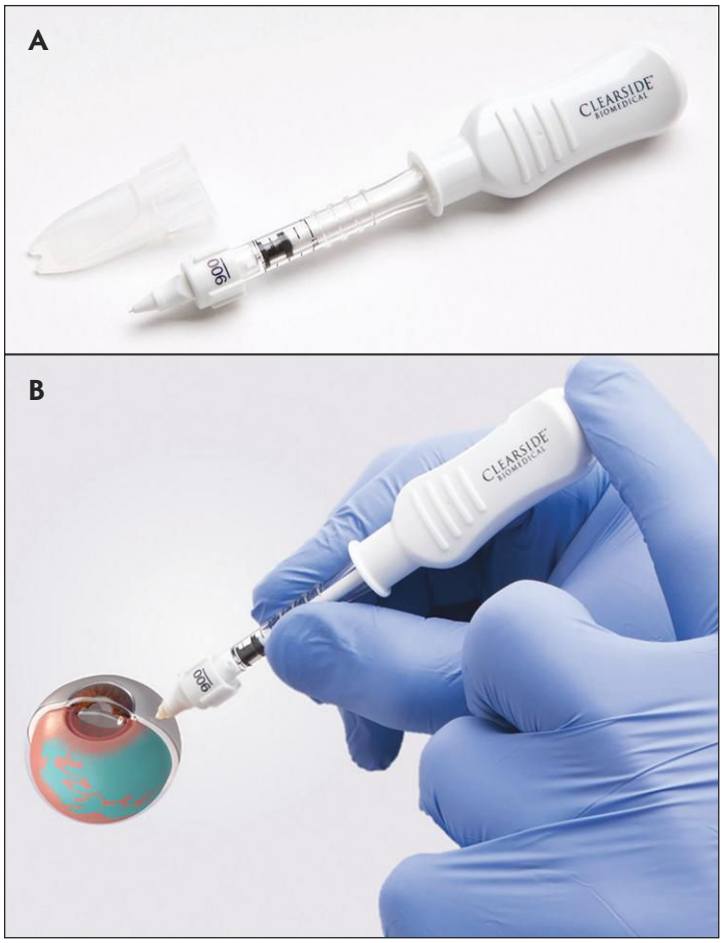

Figure 2. SCS Microinjector (Clearside Biomedical), with 900 µm needle connected (A). Illustration of SCS Microinjector injecting perpendicularly into an eye with top scleral layer partially removed to show injectate (teal) spreading circumferentially and peripherally around the globe (B).

SCS is naturally collapsed and requires some pressure to be accessed. During the process of injection, as the SCS gradually begins to open, a loss of resistance to flow is felt through the syringe system as the injectate gradually flows into the SCS and it expands. During the procedure, if continued resistance is experienced by the physician, the needle can be switched to the longer 1,100 µm needle for additional depth to access the SCS.

Preclinical studies with the SCS Microinjector have shown expansion of the SCS posteriorly to the optic nerve head in animal models,[12] and clinical studies have shown acute opening of the SCS in humans.[13] In a preclinical study using the SCS Microinjector for suprachoroidal delivery of a small molecule suspension, there were similar durable drug levels in the central vs peripheral chorioretinal tissues,[14] supporting the potential to treat both peripheral retinal and macular disorders.

The SCS Microinjector has been assessed in more than 1,200 suprachoroidal injections across multiple retinal disorders with a safety profile comparable to intravitreal (IVT) injections. It has been well accepted by physician investigators. A procedural performance study, which included a user survey and analysis of procedural variables, showed that 84% (31/37) of physician investigators did not perceive suprachoroidal injections to be meaningfully more challenging than other types of ocular injections, following their first use of the microinjector device in a patient, and that the 2 needle lengths accommodate a wide range of anatomic and demographic variables.[11]

CORTICOSTEROIDS FOR SUPRACHOROIDAL USE

Uveitis, a heterogeneous group of mostly noninfectious inflammatory disorders, affects approximately 350,000 patients in the United States and more than 1 million patients globally. Uveitic macular edema, affecting approximately one-third of these patients, is the leading cause of vision loss in uveitis.

Corticosteroids, the standard of care for uveitis, are effective, but when delivered locally, as drops, periocularly, or intravitreally, are associated with significant side effects, such as cataracts, elevated intraocular pressure (IOP), and even glaucoma with long-term use. CLS-TA is a proprietary suspension of the corticosteroid triamcinolone acetonide, or TA, for suprachoroidal injection. After SC injections of TA in preclinical models, concentrations were high in the retina and choroid with limited exposure to the anterior segment; TA was detectable in chorioretinal tissues for up to 3 months (the length of these studies).[15-17] These studies demonstrate that SC delivery can compartmentalize therapy away from the anterior segment while targeting chorioretinal tissues with prolonged pharmacokinetics for durability. Pharmacodynamically, this targeting may potentiate efficacy, because one-tenth the dose of TA administered suprachoroidally demonstrated similar efficacy as the full dose administered intravitreally in a porcine model of acute uveitis.[18]

The PEACHTREE trial was the first phase 3 clinical trial for noninfectious uveitis (NIU) patients in which best-corrected visual acuity improvement was the primary efficacy endpoint; 47% of the subjects treated with 2 CLS-TA injections administered 12 weeks apart gained at least 15 ETDRS letters from baseline at 24 weeks, compared to 16% in the sham control group ($P<.001$).[19] PEACHTREE was also the first pivotal trial that included patients with all types of uveitis: anterior, posterior, intermediate, and panuveitis. In the control arm, 72% received rescue therapy compared to 14% in the CLS-TA arm, with IVT and periocular corticosteroids being most used. Adverse events of nonacute elevated IOP, defined as not occurring on the day of the injection procedure, or occurring on the day of injection and not resolving the same day, occurred in 11.5% of the CLS-TA arm and 16% of the control arm.[20]

Table 2: Development Progress of Therapeutic Entities Delivered via the SCS Microinjector Currently Under Evaluation in 6 Clinical Trials Globally

THERAPEUTIC ENTITY	INDICATION	PRECLINICAL	PHASE 1/2	PHASE 2	PHASE 3	FDA-APPROVED
CLS-AX axitinib injectable suspension for suprachoroidal use [CLEARSIDE BIOMEDICAL]	Neovascular AMD					
RGX-314 AAV-based Gene Therapy [REGENXBIO]	Neovascular AMD					
RGX-314 AAV-based Gene Therapy [REGENXBIO]	Diabetic Retinopathy					
AU-011 Viral like drug conjugate [AURA BIOSCIENCES]	Choroidal Melanoma					
XIPERE® triamcinolone acetonide injectable suspension for suprachoroidal use [BAUSCH + LOMB]	Macular edema associated with uveitis					
CLS-TA triamcinolone acetonide injectable suspension for suprachoroidal use [ARCTIC VISION]	Macular edema associated with uveitis*					
CLS-TA triamcinolone acetonide injectable suspension for suprachoroidal use [ARCTIC VISION]	Diabetic macular edema					

**Phase 3 trial to satisfy regulatory requirements for select non-US markets*

In October 2021, the FDA approved CLS-TA for the treatment of UME. Bausch + Lomb is commercializing CLS-TA (Xipere) in the United States and Canada, and Arctic Vision plans to commercialize it in greater China, South Korea, India, the ASEAN countries, Australia, and New Zealand. Currently, Arctic Vision is evaluating CLS-TA in a phase 3 trial for macular edema associated with uveitis, and in a phase 2 trial for diabetic macular edema.

THERAPIES CURRENTLY UNDER EVALUATION IN CLINICAL TRIALS

Currently, there are 6 clinical trials enrolling globally to evaluate 4 different therapeutic entities delivered to the SCS via the SCS Microinjector **(Table 2).**

Small Molecules and the Suprachoroidal Space

Neovascular age-related macular degeneration (nAMD) represents the leading cause of legal blindness in adults over 55 years old in the industrialized world. The current standard of care is IVT anti-VEGF therapy. However, clinical outcome studies of IVT anti-VEGF therapy have demonstrated that patients receive only 6 to 7 injections per year on average, resulting in mean improvement of only 1 to 3 letters in visual acuity after 1 year of treatment.[21,22]

A promising small molecule suspension currently being evaluated utilizing SC delivery is axitinib. It is a highly potent TKI that inhibits vascular endothelial growth factor receptors VEGFR-1, VEGFR-2, and VEGFR-3 at picomolar concentrations.[23] Axitinib is a more highly potent TKI than others that have been assessed in ocular clinical trials; in an animal model of neovascularization, axitinib was the most effective in inhibiting vascular growth of the TKIs sorafenib and sunitinib.[24] Multiple preclinical studies demonstrate inhibition of neovascularization in corneal, retinal, and choroidal tissues.[24-29] Axitinib has been shown not only to inhibit angiogenesis, but also regress established neovascularization in preclinical choroidal neovascularization models,[25,26] which may be more relevant to potential clinical use. Furthermore, in vitro assessment of axitinib revealed better biocompatibility with ocular cells compared to other TKIs,[30] suggesting the potential for intrinsic safety benefits.

Axitinib, with its pan-VEGF inhibition activity,[25] may have therapeutic synergies with SC delivery, with its ability to target affected posterior tissues and compartmentalize drug away from unaffected tissues. Suprachoroidally administered axitinib (CLS-AX) has shown promise in a laser-induced choroidal neovascularization model, and retinal vascular leakage model, in rats and pigs. In a rabbit model, suprachoroidal injection of CLS-AX showed an 11-fold higher mean exposure in the posterior eye cup, compared to the IVT injection. The retinal pigment epithelium-choroid-sclera and retina also showed sustained levels of CLS-AX throughout

the study after a single suprachoroidal injection.[10] These results demonstrate the favorable pharmacokinetic properties of CLX-AX delivered suprachoroidally with long-acting potential that could reduce treatment burden to nAMD patients.

Suprachoroidally injected CLS-AX is being assessed in the ongoing phase 1/2a OASIS clinical trial[31] in treatment-experienced patients with nAMD. OASIS is an open-label, dose-escalation clinical trial to assess the safety and tolerability of single doses of SC CLS-AX. The lowest planned doses of 0.03 mg and 0.1 mg CLS-AX were found to be well tolerated in patients and no serious adverse events were observed. The trial has advanced to cohort 3, using a dose of 0.5 mg CLS-AX.[32]

Gene Therapy and the Suprachoroidal Space

Several routes of administration have been used for ophthalmic gene therapy. Historically, the standard method involves operating room–based pars plana vitrectomy (PPV) followed by retinotomy and injection of the vector into the subretinal space. Subretinal administration creates a temporary limited retinal detachment, or "bleb," but facilitates direct delivery to the RPE and photoreceptors. Currently, the only approved retinal gene therapy and most investigational retinal gene therapies are administered via PPV at a limited number of ocular gene therapy treatment centers. During PPV, there are iatrogenic risks associated with retinotomy and subretinal bleb, especially in eyes with already compromised retina and RPE. Consequently, the surgery requires extensive training, and the limited number of ocular gene therapy centers creates patient access issues.

Suprachoroidal delivery of both nonviral and viral vectors recently has been under investigation.[12,33-38] Unlike subretinal administration, SC administration does not require detachment of photoreceptors from the RPE, and consequently it avoids the risk of iatrogenic subretinal injection to an already compromised retina. A suprachoroidal injection procedure is an office-based procedure and could ultimately enhance access to care, because it would not require a specialized gene therapy surgery treatment center. In one preclinical study, SC and subretinal administration of DNA nanoparticles resulted in comparable marker gene activity in the retina and RPE-choroid.[12] In another preclinical study, SC administration of an AAV8 vector expressing an anti-VEGF Fab (RGX-314) resulted in similar expression of anti-VEGF Fab and suppression of VEGF-induced vascular leakage, as subretinal administration at the same dose.[33]

Regenxbio is currently sponsoring 2 phase 2 clinical trials assessing suprachoroidal delivery of RGX-314: the phase 2 AAVIATE trial for the treatment of nAMD, and the phase 2 ALTITUDE trial for the treatment of diabetic retinopathy. Regenxbio reported positive initial data from both clinical trials in October 2021 and is continuing to enroll patients in both trials. In ALTITUDE cohort 1, RGX-314 was well tolerated in 15 patients with no intraocular inflammation or drug-related serious adverse events at 6 months. Importantly, 47% of patients treated with RGX-314 demonstrated a ≥2-step improvement from baseline on the ETDRS diabetic retinopathy severity scale at 6 months, compared to 0% of patients in the observational control.[39] These results suggest the potential for disease modification of diabetic retinopathy with a one-time gene therapy.

> ... by both maximizing drug levels in the targeted chorioretina and minimizing levels in the anterior segment of the eye, suprachoroidal injection has the potential to facilitate efficacy and safety.

Ocular Oncology and the Suprachoroidal Space

Aura Biosciences is currently evaluating a virus-like drug conjugate, AU-011, administered via the SCS for the treatment of choroidal melanoma (CM), the most common primary intraocular tumor in adults. AU-011 is a light-activated therapeutic, utilizing a virus-like particle and approximately 200 molecules of a phthalocyanine dye. AU-011 binds selectively to cancer cells through specifically modified heparan sulfate proteoglycans on the tumor cell surface.

When AU-011 is photoactivated via nonthermal infrared laser light, it induces cell membrane disruption, acute cancer cell necrosis, and a long-term antitumor response. In a preclinical xenograft model involving implanted human choroidal melanoma cells, tumor regression was observed, and clinical proof of concept was established in treating CM via a phase 1b/2 trial using IVT injection.[40] Aura is currently sponsoring an open-label, dose-escalation, phase 2 clinical trial of AU-011 via SC administration in patients

with CM, and preliminary results support a positive safety and tolerability profile. Aura plans to share initial efficacy data of the phase 2 SC trial in late 2022. A global pivotal trial in CM with suprachoroidal delivery will initiate by the end of 2022 in 70 subjects with 2 doses of AU-011 and a sham control in early-stage disease, which includes both indeterminate lesions and small melanomas.

CONCLUSION

The suprachoroidal space is a unique ocular potential space, with exciting possible applications for unmet needs in ophthalmology. Xipere may be the first of many therapies approved for delivery suprachoroidally. These ongoing trials could demonstrate the potential of suprachoroidal delivery to advance the practice of ophthalmology. **RP**

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Flow Mechanics of Suprachoroidal Injection

A compartmentalized delivery route facilitates more targeted retinal drug delivery.

VENKATKRISH M. KASETTY, MD • LUKE G. QIN • DIEGO ESPINOSA-HEIDMANN, MD • DENNIS M. MARCUS, MD

Multiple drug-delivery routes exist for retinal therapy **(Figure 1).** Intravitreal drug delivery is the most common route used. It is the established route of anti-vascular endothelial growth factor (anti-VEGF) therapy as the first-line therapy for neovascular age-related macular degeneration (nAMD), diabetic macular edema (DME), and macular edema (ME) secondary to retinal vein occlusion (RVO). Intravitreal drug delivery has been easily adopted by retina specialists due to its proven safety, efficacy, and ease of office-based administration.

The suprachoroidal space (SCS) has recently been investigated for retinal drug delivery. It is a potential space defined as the area between the choroid and overlying sclera, approximately 35 µm thick. Similar to intravitreal injections, suprachoroidal injections are performed in the office setting with the benefits of direct delivery to the retina, choroid, and retinal pigment epithelium (RPE) without having to penetrate the internal limiting membrane (ILM) as well as limiting anterior-segment drug delivery and related side effects.[1]

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CHALLENGES WITH INTRAVITREAL INJECTIONS

Although anti-VEGF intravitreal injections have greatly improved outcomes for patients with DME, nAMD, and RVO, the frequency of injections and treatment burden remains a challenge to optimize real-world outcomes.[2-4] In addition, the Diabetic Retinopathy Clinical Research (DRCR) Network Protocol W and the PANORAMA study confirmed the role of intravitreal aflibercept in the reduction of vision-threatening consequences and in improving diabetic retinopathy (DR) severity in eyes with severe nonproliferative diabetic retinopathy (sNPDR) without DME.[5,6] As a significant number of anti-VEGF injections for DR eyes without DME are required, the retina community has not readily adopted anti-VEGF treatment in these sNPDR eyes without DME that may be otherwise observed with close follow-up. Intravitreal steroids are currently used as treatment for noninfectious ocular inflammation, and as a second-line therapy for DME and ME secondary to RVO.[7-10] However, side effects include intraocular pressure elevation, especially in "steroid responder" eyes, as well as increased rates of cataract formation.[10] Although intravitreal retinal drug delivery has been generally proven a safe, effective, and easily utilized mode of therapy, anti-VEGF treatment burden and anterior-segment side effects remain drawbacks in optimizing visual outcomes.[3,11] In addition, patient noncompliance, especially among patients with diabetes, limits real-world outcomes.

Therefore, the dogma for improving retinal pharmacotherapy has long been recognized as the need for longer acting, more durable anti-VEGF therapy. Faricimab (Vabysmo; Genentech) and the Port Delivery System with ranibizumab (Susvimo; Genentech) are intravitreal therapies recently approved by the FDA that demonstrated decreased injection burden for nAMD and DME eyes.[12-15] Intravitreal injections of gene therapy with an anti-VEGF transgene product (Adverum Biotechnologies) have shown promise in reducing treatment burden in early trials in nAMD and DME, but there was a significant inflammatory response

in the DME population in the OPTIC and INFINITY trials. Alternative delivery methods, such as subretinal and suprachoroidal drug delivery, have the potential to be longer acting routes resulting in a decreased injection burden, while also limiting anterior segment side effects as well as gene therapy–induced inflammation.

SUBRETINAL DRUG DELIVERY

Retinal gene therapy for retinal degeneration and retinal vascular disease is an exciting, potentially durable approach. Subretinal delivery has been the most evaluated route for retinal gene therapy delivery. Here, viral vectors are directly delivered to the subretinal space, targeting treatment to the RPE and outer retina. This space is immune-privileged and therefore immune reactions to the injectate are potentially limited. However, compared to other delivery methods, this method is invasive and requires a vitrectomy for administration, posing a significant barrier to administration as well as increased risks for the patient. Additionally, the injectate does not spread within the subretinal space and is typically localized to the area around the injection site.[16]

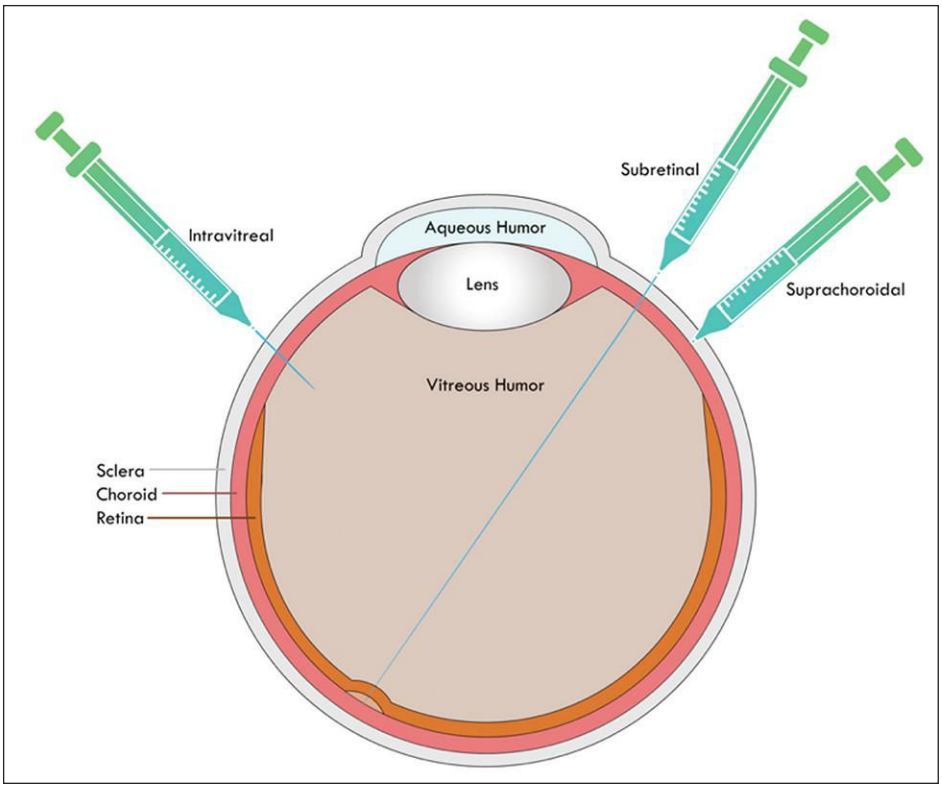


Figure 1. Retinal drug delivery routes.

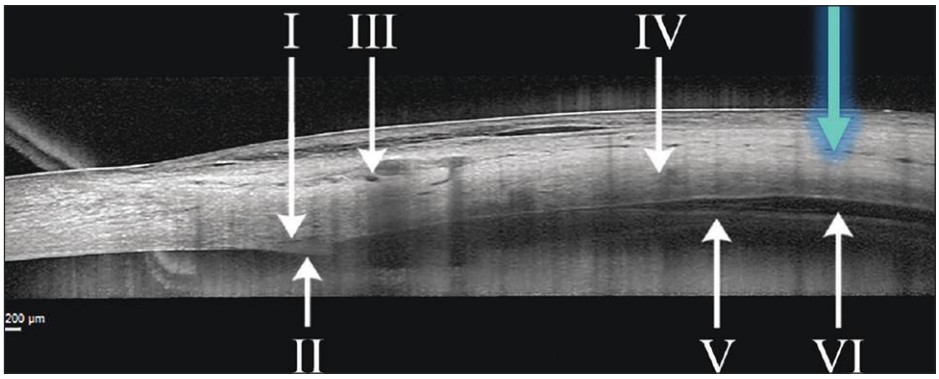


Figure 2. Anterior-segment optical coherence tomography demonstrating spread of suprachoroidal injection of triamcinolone acetonide within the suprachoroidal space 30 minutes after suprachoroidal injection.[25] *Image courtesy of Clearside Biomedical, Inc*

Voretigene neparvovec-rzyl (Luxturna; Spark Therapeutics) is the first FDA-approved gene therapy for *RPE65*-associated inherited retinal dystrophy.[17] The therapy is an *RPE65* gene-containing adeno-associated virus (AAV) vector that has demonstrated improvements in navigation, light sensitivity, and visual fields with a good safety profile over 3 to 4 years.[18] Gene therapy is also being studied for DR and AMD patients with the aim of providing an endogenous supply of anti-VEGF. This has the potential to be the next frontier in retinal therapy as a "one and done" approach for these conditions. Early clinical data using subretinal adenoviral vector anti-VEGF gene therapy (Regenxbio) indicate a significant reduction in treatment burden and encouraging safety profile in nAMD eyes previously treated with intravitreal anti-VEGF drugs.[19]

SUPRACHOROIDAL DRUG DELIVERY

Suprachoroidal delivery represents a promising minimally invasive route of a potentially durable treatment, avoiding the invasiveness of vitrectomy needed for subretinal delivery or Port Delivery System insertion. In addition to providing direct targeted therapy to the retina and choroid, suprachoroidal delivery avoids barriers such as the ILM and the creation of floaters in visual axis encountered in intravitreal drug administration. The SCS can be accessed by catheters, needles, and microneedles. Microneedle (SCS Microinjector; Clearside Biomedical) delivery allows for in-office delivery to the SCS with more control than hypodermic needles.[16] The advantages of suprachoroidal delivery

include the potential to provide a higher bioavailability to a large surface area of the diseased retina and choroid when compared to intravitreal injections.[16,20] While systemic absorption through the SCS delivery is unknown, it is likely to be limited because this injection method compartmentalizes the drug in the SCS, preventing unnecessary exposure to the anterior segment.[16,21] It is also less likely to cause a systemic immune response compared to intravitreal delivery.[22] In the INFINITY trial, the intravitreal injection of ADVM-022 vector (encoding for anti-VEGF) was therapeutically effective, but also resulted in significant intraocular inflammation and hypotony in DME patients who were given a high genomic load. This led to study termination to determine the etiology of this inflammation.[23,24]

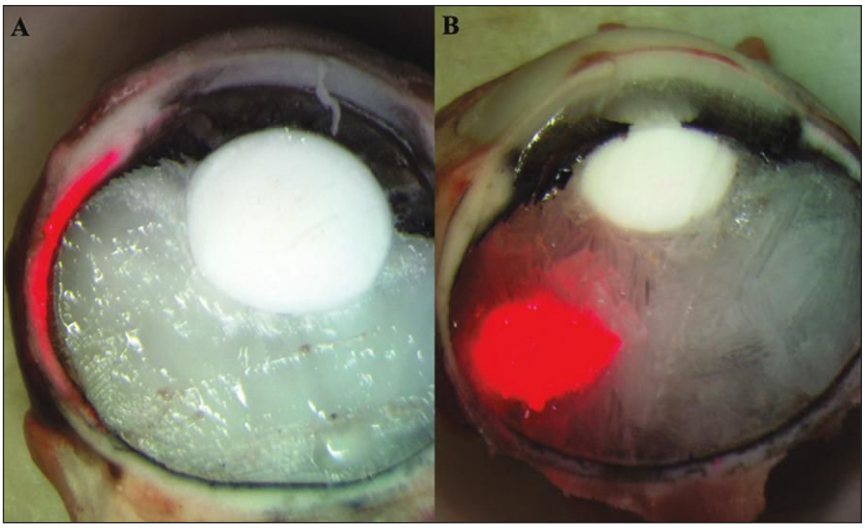


Figure 3. Distribution of dye injectate in ex vivo porcine eyes immediately frozen after (A) suprachoroidal injection and (B) intravitreal injection. *Image courtesy of Clearside Biomedical, Inc*

FLOW DYNAMICS OF SUPRACHOROIDAL INJECTIONS

Lampen et al evaluated the anatomic changes to the SCS after the suprachoroidal injection of triamcinolone acetonide (CLS-TA) for diabetic macular edema (phase 1/2 HULK study). They found immediate but transient SCS opening following injections with no significant short-term changes seen in the SCS after injection when compared to the SCS of fellow eyes **(Figure 2).**[25] However, the TANZANITE trial demonstrated significant short-term SCS expansion after suprachoroidal CLS-TA for macular edema secondary to retinal vein occlusion.[26] Therefore, data on long-term anatomic and physiologic changes to the SCS after drug delivery remain preliminary and speculative.

The flow dynamics of suprachoroidal delivery in ex vivo porcine eyes using multimodal imaging demonstrate that immediately after an SCS injection, the injectate quickly spread posteriorly from the scleral spur to the macula **(Figure 3A)** compared to a localization of the injectate bolus within the vitreous **(Figure 3B).** Therefore, immediately after SCS delivery, the same injectate is exposed to a greater surface area of retinal tissue compared to that from an intravitreal injection. Over time, the injectate also demonstrates a posterior and circumferential spread within the SCS **(Figure 4).** Endoscopic visualization of the injectate demonstrated similar posterior and circumferential spread within the SCS **(Figure 5).** These novel imaging modalities emphasize the potential benefits of suprachoroidal therapy — a targeted delivery to affected chorioretinal tissues, compartmentalization away from unaffected tissues for safety, and superior bioavailability when compared to intravitreal injections.[27] Clinical applications of suprachoroidal delivery of RGX-314 in a DR eye from the ALTITUDE trial **(Video 1)** supports these preclinical findings.

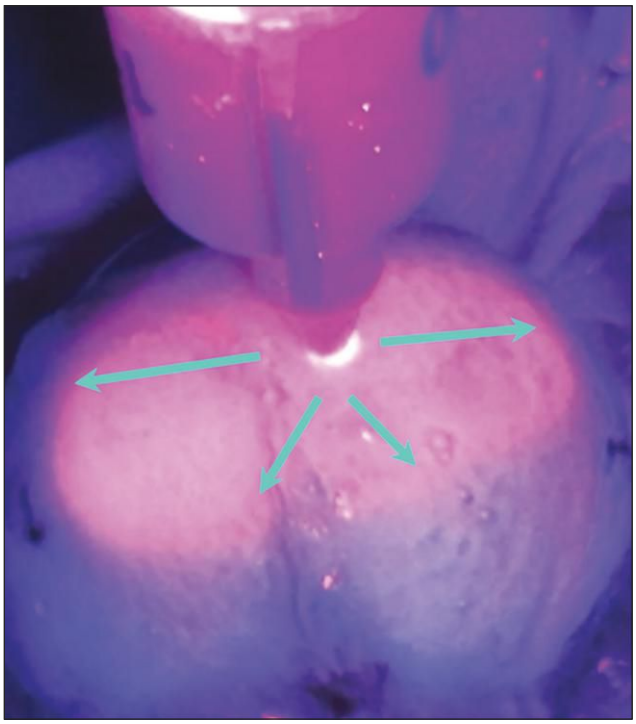


Figure 4. Injection of fluorescing dye under ultraviolet light within the suprachoroidal space in an ex vivo porcine eye demonstrates posterior and circumferential spread. *Image courtesy of Clearside Biomedical, Inc*

SUPRACHOROIDAL STEROID DELIVERY

Suprachoroidal steroid delivery proves to be an interesting alternative to intravitreal steroids. Xipere (Clearside Biomedical), a suprachoroidal triamcinolone acetonide formulation (CLS-TA), has recently been approved for macular edema (ME) secondary to noninfectious uveitis (NIU).[28] The PEACHTREE trial demonstrated that CLS-TA resulted in significant improvements in best corrected visual acuity (BCVA) without increased rates of cataract formation or elevated intraocular pressure in ME secondary to NIU.[29] The

MAGNOLIA trial demonstrated that 50% of patients treated with CLS-TA for ME secondary to NIU did not require rescue medication for up to 9 months after treatment.[30] Additionally, the TYBEE study demonstrated similar visual acuity results with a modest anatomic benefit and reduced treatment burden at 24 months in DME eyes treated with suprachoroidal CLS-TA and intravitreal aflibercept when compared to intravitreal aflibercept monotherapy.[31] Tayyab et al further demonstrated that CLS-TA results in statistically significant short-term improvements in BCVA and central subfield thickness in treatment-resistant DME.[32]

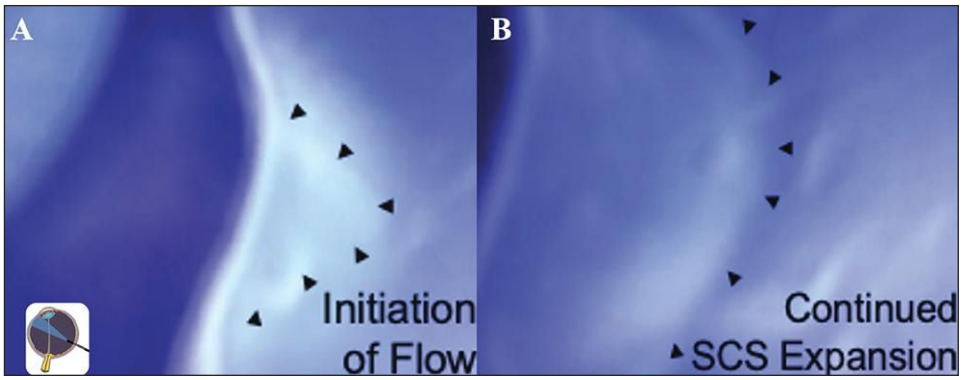


Figure 5. Endoscopic visualization of suprachoroidal injection showing (A) deformation as injectate is started and (B) continued suprachoroidal space expansion as injectate delivered with the black arrows demonstrating inherent boundary of suprachoroidal space. Adapted from Marcus D. Comparison of suprachoroidal and intravitreal injection flow mechanics analyzed via multimodal imaging. Presented at The Retina Society Annual Meeting, 2021. *Image courtesy of Clearside Biomedical, Inc*

SUPRACHOROIDAL GENE DELIVERY

The SCS is a unique target for gene therapy due to its immune privilege.[16] Multiple clinical trials are under way evaluating suprachoroidal delivery of anti-VEGF gene therapy for both DR without DME and nAMD. Six-month phase 2 ALTITUDE trial data evaluating suprachoroidal RGX-314, an AAV8 vector with an anti-VEGF encoding gene, for DR without CI-DME demonstrated exceptional DRSS improvement rates **(Figure 6),** which were comparable to the improvements seen in severe NPDR eyes in the RIDE/RISE and PANORAMA trials.[5,33,34] Importantly, no steroid prophylaxis was administered. Early phase 2 data for suprachoroidal RGX-314 for nAMD in the AAVIATE trial demonstrated promise as well compared to ranibizumab (Lucentis; Genentech) alone.[35] Given the gene therapy–induced autoimmune intraocular inflammation and hypotony reported in the INFINITY trial with intravitreal delivery, the long-term safety and efficacy of suprachoroidal anti-VEGF gene therapy needs continued evaluation.[23,24]

CONCLUSIONS

Suprachoroidal injections have been met with good reception from physician investigators, with 84% not perceiving these as more challenging than other ocular injections.[36] It is an exciting avenue of retinal drug delivery because it affords potential advantages over intravitreal and subretinal drug

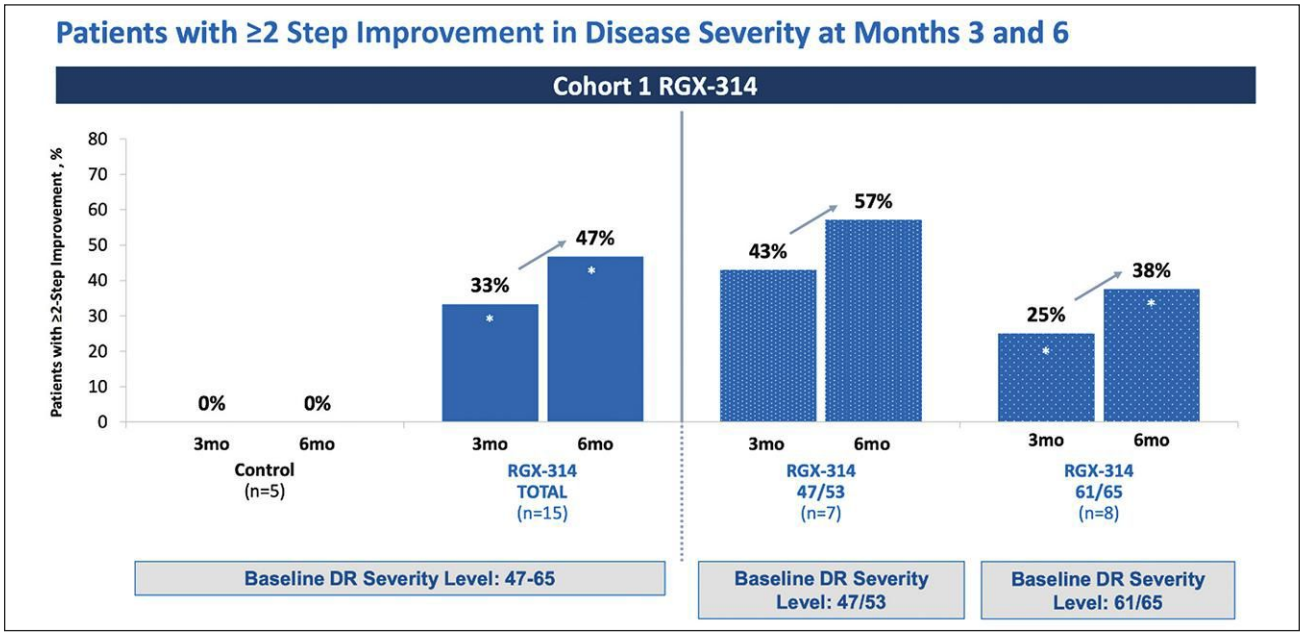
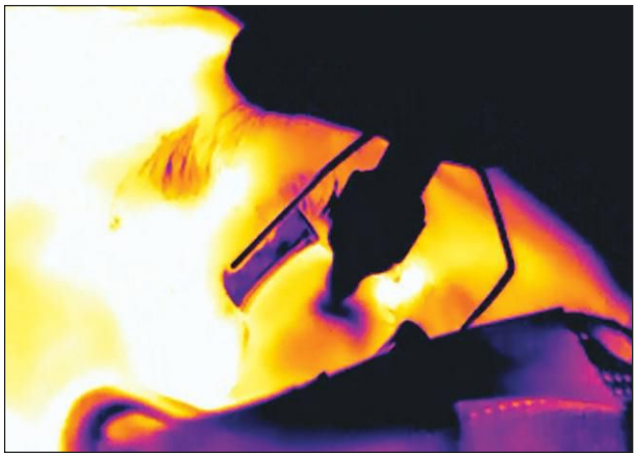


Figure 6. Six-month ALTITUDE trial phase 2 data of diabetic retinopathy eyes without center-involved diabetic macular edema treated with suprachoroidal RGX-314 (Regenxbio) demonstrating exceptional Diabetic Retinopathy Severity Score improvement rates comparable to those seen in severe nonproliferative diabetic retinopathy eyes in RIDE/RISE and PANORAMA trials. *Image courtesy of Regenxbio*



Video 1. In this video, available with this article at www.retinalphysician.com, Dennis Marcus, MD, administers suprachoroidal RGX-314 in a patient with diabetic retinopathy as part of the ALTITUDE trial.

delivery. Suprachoroidal steroid therapy for DME and CME from NIU has already been proven successful. Short-term studies on suprachoroidal gene therapy for DR and nAMD appear promising in reducing treatment burden and addressing noncompliance, especially in diabetic patients. Further study will evaluate the long-term efficacy and safety of suprachoroidal retinal drug and gene therapy delivery. **RP**

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Suprachoroidal Delivery as a Novel Avenue for Retinal Gene Therapy

Clinical trials are investigating suprachoroidal gene therapy for wet AMD and DR.

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The daily impacts of vision impairment due to debilitating retinal diseases, such as age-related macular degeneration (AMD) and diabetic retinopathy (DR), are widespread. These diseases are responsible for acquired vision loss among working adults between the ages of 20 and 74 years and elderly patients older than 60 years of age.[1] Globally, approximately 126.6 million individuals are negatively impacted by DR, and another 187 million by AMD.[1]

There are several US Food and Drug Administration (FDA)-approved therapeutics for wet AMD and DR, including ranibizumab and aflibercept. However, due to the short half-lives of these anti-VEGF therapeutics, patients need frequent intravitreal injections for disease control, which leads to high treatment burden.[2,3] There is an unmet need to improve the potency of therapeutics while reducing patient burden through improved drug delivery and sustainability, which is currently being explored via clinical trials.[2] Ocular gene therapy is an emerging sustained delivery treatment option for patients with retinal diseases.[4] The suprachoroidal space (SCS), the space between the sclera and choroid, is the proposed injection site for gene therapy, because it has potential to be less invasive while also providing adequate gene expression to control disease. This article reviews the SCS, the viral vectors available for gene therapy, and current clinical trials investigating unique suprachoroidal gene therapy therapeutics.

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THE SUPRACHOROIDAL SPACE

The SCS presents as a small pocket between the sclera and choroid of the eye and is being investigated as an injection site for posterior-segment disease therapeutics.[5] The location of this space with respect to the blood–retinal barrier, the scleral spur, and optic nerve may allow for decreased off-target binding and immune responses to injected therapeutics.[2,5]

It has been demonstrated that fluid injected into this space flows posteriorly toward the choroid and RPE, allowing for targeted drug administration.[2,5] Successful treatment of retinal diseases relies on sufficient bioavailability near the retinal pigment epithelium (RPE) tissue.[5] Thus, suprachoroidal injections may result in increased bioavailability within diseased tissue, reducing therapeutic dosage required to achieve favorable outcomes.

The SCS can be visualized as a hyperreflective band via enhanced-depth imaging optical coherence tomography (EDI-OCT) and swept-source OCT, but it is difficult to view prior to suprachoroidal injection because it is typically collapsed due to intraocular pressure (IOP). Reliable visualization of the SCS is achieved following suprachoroidal injection as the space expands, holding up to 1 mL of fluid.[5-7] Detection rates of SCS can be influenced by age, choroidal thinning from retinal diseases, and choroidal vessel protein leakage into the SCS.[6,7]

Access to the SCS via sclerotomy followed by catheter or cannula placement allows for improved visualization and subsequent ease of therapeutic administration

within the space.[8] Treatment administration within the SCS can also be done in a clinic setting using either hypodermic needles or hollow microneedles. Hypodermic needles are readily available and require increased precision and attention to applied force due to limited SCS access.[5] Microneedles inject medication directly into the SCS without retinal penetration because they contain scleral-length needles.[5]

Favorable phase 3 clinical trial results have demonstrated efficacy and safety of the SCS as an injection site for retinal disease treatment. The recent FDA approval of triamcinolone acetonide injectable suspension as the first medicine delivered via suprachoroidal injection (Xipere; Bausch + Lomb) has shown positive results.[9] Further clinical studies are required to determine efficacy, safety, and durability of therapeutic administration in the SCS.

GENE THERAPY VECTORS

The eye is an immune-privileged, compartmentalized organ that permits localized medication delivery and is a target for gene therapy. Viral vectors ensure long-term treatment with adequate gene expression, providing an alternative treatment avenue for retinal diseases.[4] Gene therapy delivery requires one of 3 viral vectors: adeno-associated viruses (AAVs), adenovirus (Ad) vectors, and lentiviral vectors. Determining which viral vector to utilize as a therapeutic mechanism for retinal diseases is based on longevity of gene expression to significantly reduce treatment burden. The goal of gene therapy is to provide a single treatment with minimal risk of immune response.[10]

Because they can carry large genomes (4.7 kbp) encapsulated in proteins, AAVs are the most utilized gene therapy delivery mechanism. These vectors reduce the risk of host immune response, but they have the ability to alter the host's genome.[11] AAVs present increased gene expression in nondividing cells, which is significantly more than current anti-VEGF drugs.[10] Gene expression is effectively altered within RPE cells and photoreceptors; thus, serotypes can easily be engineered.[12]

Ad vectors consist of a large genome (~36 kbp) encapsulated in a protein shell.[13] These vectors are less commonly used in gene therapy because they do not integrate into the host cell's genome, limiting their expression lifespan.[11] Ad vectors also have a higher risk of mild inflammation due to host cell immune responses.[11] Additionally, immunogenicity is slightly higher among Ad vectors compared to AAVs.[10]

Lentiviral vectors are composed of single-stranded RNA as opposed to DNA like AAVs and Ad vectors.[11] These vectors can integrate into the host cell's genome to ensure longevity of gene expression.[6] Due to the potential risk of mutagenesis associated with lentiviral vectors, adverse reactions may be increased.[6]

PHASE 2 STUDIES

ALTITUDE, a phase 2 study, is currently evaluating the safety, efficacy, and tolerability of a single dose of NAV AAV8 vector encoding a transgene for anti-VEGF fab in patients with DR without center-involved diabetic macular edema (CI-DME) who suffer from moderate to severe nonproliferative DR (NPDR) or mild proliferative DR (PDR).[14] In this multicenter, open-label, randomized, controlled dose-escalation trial, eyes were placed into 1 of 3 treatment groups: a 3:1 ratio of single dose 2.5 x 10^{11} genomic copies per eye (GC/eye) with observational control; a 3:1 ratio of a single dose of 5 x 10^{11} GC/eye with observational control; or a single dose of 5 x 10^{11} GC/eye in patients positive for neutralizing antibody (NAb).[14]

> The suprachoroidal space ... is the proposed injection site for gene therapy, because it has potential to be less invasive while also providing adequate gene expression to control disease.

Preliminary data from cohort 1 demonstrate that the single dose of AAV8 vector encoding a transgene for anti-VEGF fab was well tolerated in 15 patients. On the Early Treatment Diabetic Retinopathy Study–Diabetic Retinopathy Severity Scale (ETDRS-DRSS), 33% of patients demonstrated a 2-step or greater improvement compared to 0% improvement in the observational control. Notably, 1 patient demonstrated a 4-step improvement in ETDRS-DRSS.[14] Three of 7 NPDR patients (43%) and 2 of 8 PDR patients (25%) demonstrated a 2-step or greater improvement 3 months after study

drug administration. One serious adverse event (SAE) was reported in cohort 1, occurring in the patient's untreated fellow eye and was determined to be unrelated to the study drug.[14] One patient experienced an adverse event (AE) of episcleritis, but resolved following topical corticosteroid therapy. Intraocular inflammation (IOI) was not observed and additional AEs in the study eye were mild and not drug related.[14]

It has been demonstrated that fluid injected into this space flows posteriorly toward the choroid and RPE, allowing for targeted drug administration.

Another phase 2 study, AAVIATE, is an active-controlled, dose-escalation trial that is evaluating the safety, efficacy, and tolerability of a single dose of NAV AAV8 vector encoding a transgene for anti-VEGF fab in wet AMD patients.[15] Eyes were randomized into 1 of 3 treatment arms: a 3:1 ratio of single dose $2.5x10^{11}$ GC/eye with monthly 0.5 mg ranibizumab IVT injection control; a 3:1 ratio of single dose $5x10^{11}$ GC/eye with monthly 0.5 mg ranibizumab IVT injection control; and a 3:1 ratio of single dose $5x10^{11}$ GC/eye with monthly 0.5 mg ranibizumab IVT injection control in NAb-positive patients.[9] Extension study for AAVIATE will encompass cohorts 4 and 5; 15 patients will be dosed with $1x10^{12}$ GC/eye and 20 NAb-positive patients will be dosed with $1x10^{12}$ GC/eye, respectively.[9]

At 6 months, 14 patients demonstrated visual acuity stability with a mean best-corrected visual acuity (BCVA) change of -2.8 letters (95% CI: -7.0, 1.4) and central retinal thickness (CRT) stability with a mean change of -2.5 µm (-27.1, 22.0) measured from day 1.[15] Five patients in the ranibizumab arm demonstrated a mean BCVA change of +6.8 letters (-3.3, 16.9) and stable CRT values with a mean change of -22.2 µm (-41.6, -2.8) at 6 months measured from day 1.[9] Over 6 months, a 75.9% reduction in anti-VEGF treatment burden was demonstrated in cohort 1 patients as they received an average of 1.2 injections. Additionally, 4 patients received no treatments with a mean change of BCVA and CRT values remaining stable, +1.3 letters (-5.7, 8.2) and -5.8 µm (-49.5, 38.0), respectively.[15] Study eye treatment-emergent AEs (TEAE) included mild conjunctival hemorrhage, and worsening wet AMD, with 4 cases of mild IOI.

One-time gene therapy in the SCS shows promise as a potential treatment option for patients with retinal diseases. The ongoing phase 2 studies AAVIATE and ALTITUDE will further elucidate the efficacy, durability, and safety of SCS-administered gene therapy for the treatment of wet AMD and DR. **RP**

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Light-activated Suprachoroidal Therapy for the First-line Treatment of Indeterminate Lesions and Small Choroidal Melanoma

This novel approach could be applied to various ocular oncology indications.

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Choroidal melanoma is the most common primary intraocular tumor. Based on the Collaborative Ocular Melanoma Study (COMS) classification, one of two size-based classification systems, it is classified into 3 sizes: small (1-2.5 mm in thickness, 5-16 mm in the largest basal dimension), medium (2.5-10 mm in thickness, 16 mm in the largest basal dimension) and large (>10 mm in thickness, >16 mm in the largest basal dimension).[1,2] Choroidal nevus was described as <1 mm in thickness and <5 mm in size.[1,2]

Considering how choroidal nevus evolves into melanoma, there is an overlap in size between nevus and melanoma without absolute cutoffs.[3] Over the years, several studies have explored clinical and multimodal imaging features to differentiate the choroidal nevus from the small choroidal melanoma.[4-6] Tumor thickness >2 mm, subretinal fluid, orange pigment, tumor location <3 mm to the optic disc, presence of visual symptoms, and ultrasonographic hollowness are well established risk factors for growth.[4-6] These measures are used as surrogate for predicting the growth and hence the diagnosis of choroidal melanoma, whereas the presence of drusen or intraretinal fluid shows chronicity of the lesion that favors the diagnosis of choroidal nevus.[4-6] The term "indeterminate lesion" is used for borderline lesions that cannot be definitively diagnosed as melanoma but require close follow-up to confirm that the lesion is already a small melanoma or has evolved into melanoma.[7]

Plaque radiotherapy is currently the most used treatment for small choroidal melanomas and indeterminate lesions. Because radiation lacks tumor tissue specificity, it may cause irreversible retinal damage and vision loss.[8,9] Some eyes may require enucleation due to tumor recurrence or radiation-related side effects. A review of 1,780 small choroidal melanomas (3 mm in thickness) treated with plaque radiotherapy showed a local tumor control rate of 93.5% at 5 years and 90% at 10 years.[10]

By Kaplan-Meier analysis, visual loss following plaque radiotherapy (3 Snellen lines) was 10% at 1 year, 39% at 5 years, and 49% at 10 years; severe vision loss (20/200 or >6 Snellen lines) was 7% at 1 year, 39% at 5 years, and 54% at 10 years.[10] The need for enucleation was 4% at 5 years and 7.6% at 10 years.[10] Melanoma-associated metastasis was observed 0.2% at 1 year, 4.5% at 5 years, and 8.8% at 10 years.[10] There is a high unmet need for a new vision-preserving first-line treatment option for indeterminate lesions and small choroidal melanomas.

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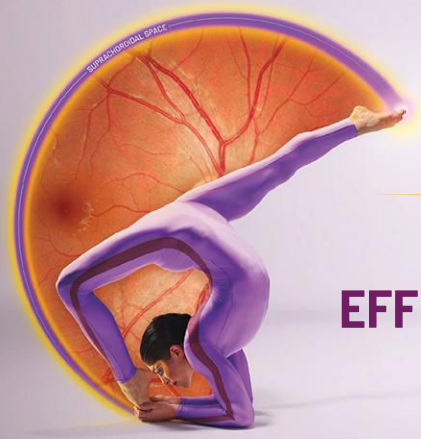

XIPERE®
(triamcinolone acetonide
injectable suspension) 40 mg/mL

IN THE MANAGEMENT OF UVEITIC MACULAR EDEMA

XIPERE® DEMONSTRATED PROVEN EFFICACY THROUGH INNOVATIVE DRUG DELIVERY VIA THE SUPRACHOROIDAL SPACE[1-5]

SIGNIFICANT AND SUSTAINED BCVA IMPROVEMENTS[1-3*]

Improvement of ≥15 ETDRS letters from baseline at Week 24 in 47% of XIPERE® patients compared with 16% in the control group (n=96 and n=64, respectively; *P*<0.01) in the pivotal trial[2]

XIPERE DELIVERED DURABILITY[3†]

344 days was the median time to rescue for patients treated with XIPERE (n=28) in an observational extension study

Additionally, 50% of patients treated with XIPERE completed the study by reaching the Week 48 visit without rescue medication

PROVEN SAFETY PROFILE

Assessed in 3 clinical studies: PEACHTREE, MAGNOLIA, and AZALEA[2,3,6]

SCAN TO DISCOVER MORE DATA AT
XIPERE.COM

J-CODE (J3299) NOW AVAILABLE FOR XIPERE®
EFFECTIVE JULY 1, 2022

*Phase 3 Study Design: 6-month, randomized, multicenter, double-masked, sham-controlled study in patients with macular edema associated with anterior-, intermediate-, posterior-, or pan-uveitis. After a 2-week screening period, eligible patients returned to the clinic for the baseline visit (Day 0) when they were randomly assigned in a 3:2 ratio to treatment or control. The control group underwent a sham procedure to maintain masking. Patients were treated at baseline and week 12. The primary efficacy endpoint was the proportion of patients in whom best corrected visual acuity (BCVA) had improved by ≥ 15 letters from baseline after 24 weeks of follow-up.[2]

†24-Week Extension Study Design: Multicenter, non-interventional, 6-month extension study for patients who successfully completed the Phase 3 study without requiring rescue treatment. The final visit of the Phase 3 study was the crossover visit (Day 0) of this study with follow-up visits conducted every 6 weeks.[3]

Indication

XIPERE® (triamcinolone acetonide injectable suspension) for suprachoroidal use is a corticosteroid indicated for the treatment of macular edema associated with uveitis.

Important Safety Information

Patients should be monitored following injection for elevated intraocular pressure. See Dosage and Administration instructions in full Prescribing Information.

- XIPERE is contraindicated in patients with **active or suspected ocular or periocular infections** including most viral diseases of the cornea and conjunctiva, including active epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, varicella, mycobacterial infections, and fungal diseases.
- XIPERE is contraindicated in patients with known **hypersensitivity to triamcinolone acetonide** or any other components of this product.
- Use of corticosteroids may produce cataracts, increased intraocular pressure, and glaucoma. Use of corticosteroids may enhance the establishment of secondary ocular infections due to bacteria, fungi, or viruses, and should be used cautiously in patients with a history of ocular herpes simplex.
- Hypothalamic-pituitary-adrenal (HPA) axis suppression, Cushing's syndrome, and hyperglycemia can occur following administration of a corticosteroid. Monitor patients for these conditions with chronic use.
- In controlled studies, the most common ocular adverse reactions were increased ocular pressure, non-acute (14%), eye pain, non-acute (12%), cataract (7%), increased intraocular pressure, acute (6%), vitreous detachment (5%), injection site pain (4%), conjunctival hemorrhage (4%), visual acuity reduced (4%), dry eye (3%), eye pain, acute (3%), photophobia (3%), and vitreous floaters (3%), and in 2% of patients: uveitis, conjunctival hyperaemia, punctate keratitis, conjunctival oedema, meibomianitis, anterior capsule contraction, chalazion, eye irritation, eye pruritus, eyelid ptosis, photopsia, and vision blurred.

  The most common non-ocular adverse event was headache (5%).
- Corticosteroids should be used during pregnancy or nursing only if the potential benefit justifies the potential risk to the fetus or nursing infant.

To report SUSPECTED ADVERSE REACTIONS, contact Bausch + Lomb at 1-800-321-4576 or FDA at 1-800-FDA-1088 or visit www.fda.gov/medwatch.

Please see brief summary of full Prescribing Information on adjacent page.

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BRIEF SUMMARY OF PRESCRIBING INFORMATION
This Brief Summary does not include all the information needed to use XIPERE™ safely and effectively. See full Prescribing Information for XIPERE™.

XIPERE™ (triamcinolone acetonide injectable suspension), for suprachoroidal use

Initial U.S. Approval: 1957

INDICATIONS AND USAGE

XIPERE™ (triamcinolone acetonide injectable suspension) 40 mg/mL is indicated for the treatment of macular edema associated with uveitis.

CONTRAINDICATIONS

4.1 Ocular or Periocular Infections XIPERE™ is contraindicated in patients with active or suspected ocular or periocular infections including most viral diseases of the cornea and conjunctiva, including active epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, varicella, mycobacterial infections, and fungal diseases.

4.2 Hypersensitivity XIPERE™ is contraindicated in patients with known hypersensitivity to triamcinolone acetonide or any other components of this product.

WARNINGS AND PRECAUTIONS

5.1 Potential Corticosteroid-Related Effects Use of corticosteroids may produce cataracts, increased intraocular pressure, and glaucoma. Use of corticosteroids may enhance the establishment of secondary ocular infections due to bacteria, fungi, or viruses. Corticosteroids should be used cautiously in patients with a history of ocular herpes simplex. Corticosteroids should not be used in patients with active ocular herpes simplex.

5.2 Alterations in Endocrine Function Hypothalamic-pituitary-adrenal (HPA) axis suppression, Cushing's syndrome, and hyperglycemia can occur following administration of a corticosteroid. Monitor patients for these conditions with chronic use. Corticosteroids can produce reversible HPA axis suppression with the potential for glucocorticosteroid insufficiency after withdrawal of treatment. Drug induced secondary adrenocortical insufficiency may be minimized by gradual reduction of dosage. This type of relative insufficiency may persist for months after discontinuation of therapy; therefore, in any situation of stress occurring during that period, hormone therapy should be reinstituted. Metabolic clearance of corticosteroids is decreased in hypothyroid patients and increased in hyperthyroid patients. Changes in thyroid status of the patient may necessitate adjustment in dosage.

ADVERSE REACTIONS

6.1 Clinical Trials Experience Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. XIPERE™ was studied in a multicenter, randomized, sham-controlled, double-masked study in patients with macular edema associated with uveitis. Table 1 summarizes data available from the clinical trial for XIPERE™ treated patients and control patients. The most common ocular (study eye) adverse reactions occurring in ≥ 2% of patients and nonocular adverse reactions occurring in ≥ 5% of patients are shown in Table 1.

Adverse Reaction	XIPERE™ (N = 96) n (%)	Control (N = 64) n (%)
Ocular		
Increased intraocular pressure, non-acute [a,b]	13 (14%)	9 (14%)
Eye pain, non-acute [b]	11 (12%)	0
Cataract [c]	7 (7%)	4 (6%)
Increased intraocular pressure, acute [a, d]	6 (6%)	0
Vitreous detachment	5 (5%)	1 (2%)
Injection site pain	4 (4%)	2 (3%)
Conjunctival haemorrhage	4 (4%)	2 (3%)
Visual acuity reduced	4 (4%)	1 (2%)
Dry eye	3 (3%)	1 (2%)
Eye pain, acute [d]	3 (3%)	0
Photophobia	3 (3%)	0
Vitreous floaters	3 (3%)	0
Uveitis	2 (2%)	7 (11%)
Conjunctival hyperaemia	2 (2%)	2 (3%)
Punctate keratitis	2 (2%)	1 (2%)
Conjunctival oedema	2 (2%)	0
Meibomianitis	2 (2%)	0
Anterior capsule contraction	2 (2%)	0
Chalazion	2 (2%)	0
Eye irritation	2 (2%)	0
Eye pruritus	2 (2%)	0
Eyelid ptosis	2 (2%)	0
Photopsia	2 (2%)	0
Vision blurred	2 (2%)	0
Non-ocular		
Headache	5 (5%)	2 (3%)

[a] Includes intraocular pressure increased and ocular hypertension [b] Defined as not occurring on the day of the injection procedure, or occurring on the day of the injection procedure and not resolving the same day [c] Includes cataract, cataract cortical, and cataract subcapsular [d] Defined as occurring on the day of the injection procedure and resolving the same day

USE IN SPECIAL POPULATIONS

8.1 Pregnancy Risk Summary There are no adequate and well-controlled studies with XIPERE™ in pregnant women to inform drug-associated risks. In animal reproductive studies from the published literature, topical ocular administration of corticosteroids has been shown to produce teratogenicity at clinically relevant doses. There is negligible systemic XIPERE™ exposure following suprachoroidal injection [see Clinical Pharmacology (12.3)]. Corticosteroids should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. Animal Data Animal reproduction studies using XIPERE™ have not been conducted. In animal reproductive studies from the published literature, topical ocular administration of corticosteroids to pregnant mice and rabbits during organogenesis has been shown to produce cleft palate, embryofetal death, herniated abdominal viscera, hypoplastic kidneys and craniofacial malformations.

8.2 Lactation Risk Summary It is not known whether ocular administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in human milk. Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for XIPERE™ and any potential adverse effects on the breastfed infant from XIPERE™. There are no data on the effects of XIPERE™ on milk production.

8.4 Pediatric Use Safety and effectiveness of XIPERE™ in pediatric patients have not been established.

8.5 Geriatric Use No overall differences in safety or effectiveness have been observed between elderly and younger patients following XIPERE™ administration.

NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis No information is available on the carcinogenic potential of triamcinolone acetonide.

Mutagenesis No information is available on the mutagenic potential of triamcinolone acetonide.

Fertility No information is available on the effect of triamcinolone acetonide on fertility.

Manufactured for: Clearside Biomedical, Inc.
900 North Point Parkway, Suite 200
Alpharetta, GA 30005 www.clearsidebio.com/patents

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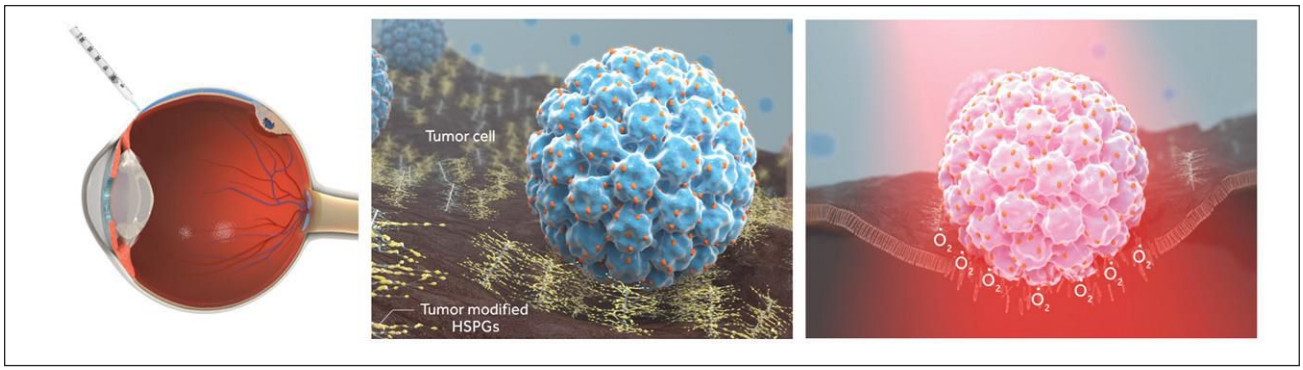

Figure 1. Virus-like drug conjugates are delivered through suprachoroidal injection (right) and bind to specifically modified HSPGs on the tumor cell surface (central). When virus-like drug conjugates are activated by 689-nm near infrared light laser, they generate singlet oxygen that disrupts the tumor cell membrane and lead to acute necrosis and anti-tumor immunity.

VIRUSES AS ANTICANCER AGENTS

AU-011 (belzupacap sarotalocan) is a novel virus-like drug conjugate (VDC), the first-in-class investigational targeted therapy in clinical development for the primary treatment of indeterminate lesions and small choroidal melanomas. AU-011 can be delivered via intravitreal or suprachoroidal injections. The phase 2 clinical trial via suprachoroidal injection is currently recruiting patients;[11] the phase 1b/2 clinical trial via intravitreal injection has completed the patient recruitment and 12-month follow-up.[12]

Virus-like particles (VLPs) are bionanomaterials that use the biocompatibility of viruses for the development of therapeutics, vaccines, and imaging tools.[13,14] They are composed of recombinant capsid proteins that may be engineered to deliver drugs efficiently to tumors. They are not associated with an increased biosafety risk, because they lack viral genetic material and have no proliferative potential.[14] VLPs derived from the human papillomavirus were reported to have a strong, restricted tropism to bind and infect most tumor-derived ovarian, lung, and melanoma cell lines in vitro and have analogous tumor-specific properties in vivo after local or intravenous injection.[15] The tumor specificity of these VLPs is driven by its binding to modified heparan sulfate proteoglycans (HSPGs) found on the tumor cell surface.[15] Tumor cells evolve HSPG modification patterns that mimic the pattern normally found on the basement membrane of damaged epithelial tissues. It has been described that N-sulfation and, to a lesser degree, 6-O sulfation, are important sulfation patterns for the binding specificity of the VLP to this unique cancer cell receptor.[15-17]

MECHANISM OF ACTION OF NOVEL INFRARED DYE-CONJUGATED VIRUS-LIKE DRUG CONJUGATE

AU-011 is a VDC based on recombinant VLP derived from the human papillomavirus conjugated to a phthalocyanine-based photosensitizer (Irdye 700DX; LI-COR Biosciences) that is activated by 689-nm near-infrared light **(Figure 1).**

The anti-cancer properties of AU-011 were assessed by using a panel of ovarian, lung, breast, cervical, head and neck, and bladder cancers, and cutaneous and uveal melanoma cell lines in vitro, and AU-011 showed potent and selective anticancer activity.[18] Its anticancer activity was blocked by inhibiting its association with HSPG using heparin and binding was not observed in cells lacking surface HSPG. These results indicate that cell binding is critical for AU-011-mediated cytotoxicity. Although AU-011 can deliver hundreds of dye molecules, its tumor tropism was not affected by dye conjugation. Following intravenous administration in murine tumor models and intravitreal administration in rabbit uveal melanoma xenograft models, potent dose-dependent tumor response with histopathologically confirmed acute tumor cell necrosis was observed after photoactivation, and treatment spared the retina and adjacent ocular structures, showing its targeted effect.[15,18]

AU-011 has a novel dual mechanism of action **(Figure 2).** The first mechanism corresponds to acute tumor cell necrosis. AU-011 delivers hundreds of photosensitizer Irdye 700DX molecules that are promoted to the excited state on light activation and generate singlet oxygen. Singlet oxygen generation near the tumor cell membrane disrupts the membrane integrity of the tumor cell and causes acute tumor cell necrosis. In addition to acute tumor cell necrosis, AU-011's activity leads to immune-mediated tumor cell killing, releasing tumor neoantigens that can activate CD-8 T cells and generate long-term antitumor immunity.[19,20]

SUPRACHOROIDAL VS INTRAVITREAL DELIVERY

In a rabbit uveal melanoma xenograft model, suprachoroidal administration of AU-011 showed 5 times higher tumor exposure compared to intravitreal injection.[21] Mean tumor concentrations were 12,459±5,190 ng/mL in eyes with suprachoroidal injection vs

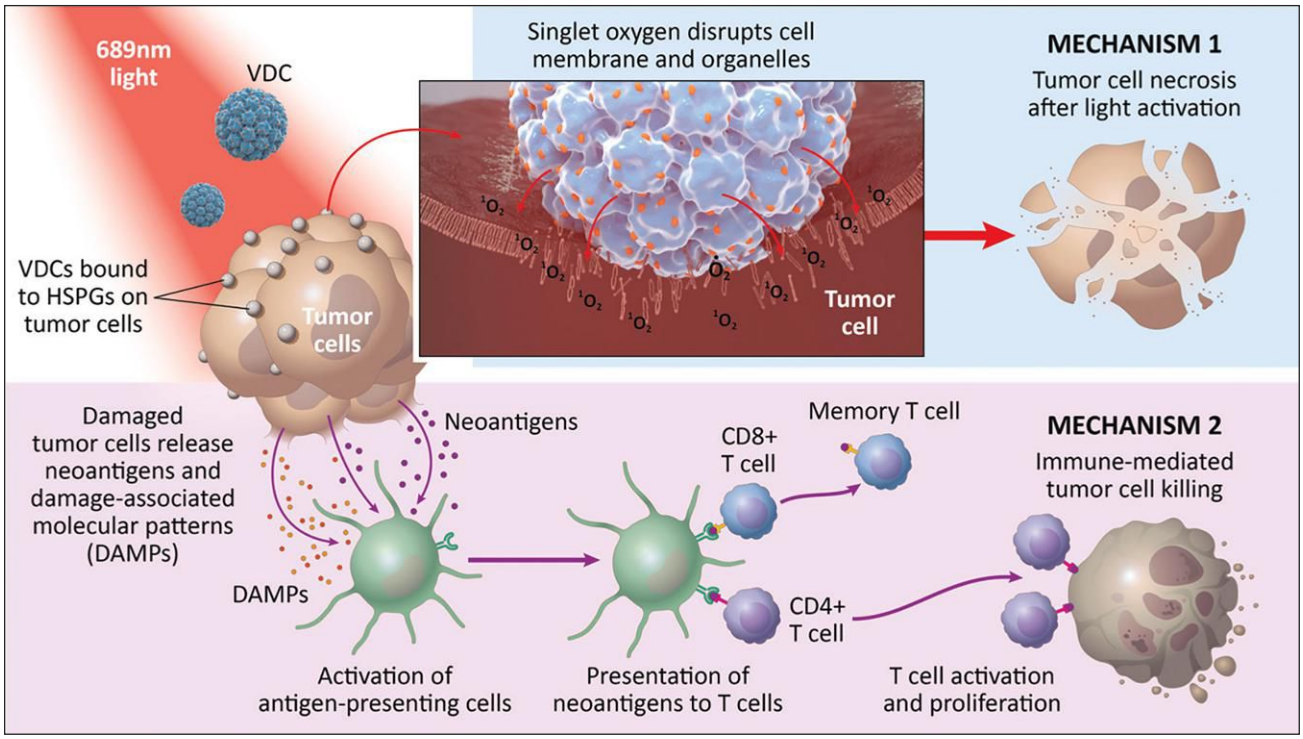

Figure 2. The dual mechanism of action of AU-011, causing acute tumor necrosis and immune activation.

1,996±421 ng/mL in the eyes with intravitreal injection. There were negligible levels of AU-011 in the vitreous in the eyes with suprachoroidal injection. Immunohistochemical AU-011 staining was observed penetrating throughout the tumor in the suprachoroidal injected group, whereas AU-011 staining was mostly localized on the apex or vitreal surface of the tumor in the intravitreally injected group. This shows that suprachoroidal administration improved tumor distribution and bioavailability and has the potential to decrease side effects such as intraocular inflammation and vitreous floaters compared to intravitreal administration. Suprachoroidal delivery may optimize the treatment parameters by shortening the interval time to laser activation (4 to 6 hours with suprachoroidal vs 6 to 8 hours with intravitreal administration) and might increase the opportunity to treat additional patient populations such as medium-sized choroidal melanoma and choroidal metastasis.

CLINICAL TRIALS WITH AU-011 VIA SUPRACHOROIDAL ADMINISTRATION

AU-011 is currently being investigated in a phase 2 clinical trial comprised of an initial open-label dose-escalation phase to determine the safety and optimal treatment regimen followed by a randomized confirmatory phase to determine the safety and efficacy via suprachoroidal administration in subjects with primary indeterminate lesions and small choroidal melanoma.[11] The initial dose-escalation phase will evaluate the safety and efficacy of single and multiple ascending doses of AU-011 via suprachoroidal administration, followed by 1 or 2 laser applications per treatment. Laser delivering light at 689 nm is applied over the choroidal tumor after 4 to 6 hours following the suprachoroidal injection of AU-011.

The open-label dose-escalation phase is currently ongoing, with 14 subjects enrolled.[23] Cohorts 1 to 5 are fully enrolled and cohort 6 is enrolling now. The study started with the first cohort group receiving 20 µg of AU-011 followed by 1 laser administration. Based on the safety and tolerability to date, the dose of AU-011 was increased to 80 µg in 2 injections in separate quadrants followed by 2 laser administrations. The treatment is being repeated for up to 3 cycles, each cycle comprised of 3 weekly treatments of 80 µg dose and 2 laser administrations. No dose-limiting toxicities or treatment-related serious adverse events have been reported. The most common side effects related to AU-011 or laser were anterior chamber cell/inflammation (23%), followed by eye pain (15.4%), and punctate keratitis (15.4%). Most adverse effects were transient and resolved without clinical sequelae.

AU-011 FOR CHOROIDAL METASTASIS

The use of light-activated VDCs represents a novel approach for the first-line treatment of choroidal tumors. AU-011 is the first VDC in clinical development with a dual mechanism of action consisting of acute necrosis followed by an immune activation that may lead to

long-term antitumor immunity. The tumor targeting is driven by the binding of the VDC to modified HSPGs on the tumor cell membrane. The favorable safety profile to date may lead to improved visual outcomes compared to the standard of care with radiotherapy, and suprachoroidal delivery may improve the therapeutic index and optimize treatment parameters compared to intravitreal administration. The preliminary safety data from the ongoing phase 2 trial using suprachoroidal administration supports the continued dose escalation to an 80 µg/day dose and up to 3 cycles of therapy.

> Suprachoroidal administration has the potential to improve the therapeutic index of AU-011 for the treatment of patients with indeterminate lesions and small choroidal melanoma.

CONCLUSION

Suprachoroidal administration has the potential to improve the therapeutic index of AU-011 for the treatment of patients with indeterminate lesions and small choroidal melanoma. Given the optimal benefit–risk profile, this novel approach could be used in many additional ocular oncology indications, such as choroidal metastasis or hemangioma. This novel route of administration could become a preferred route for treating retinal and choroidal diseases of the eye. Recently, the potential to treat choroidal metastasis of breast and lung cancer with AU-011 has been evaluated in vitro and in vivo. Rich et al noted that AU-011 can bind to, and kill, cells derived from the most common cancer types known to metastasize to the choroid, which supports further clinical development of AU-011.[22] **RP**

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New Developments in Suprachoroidal and Subretinal Drug Delivery Technology

Trials in humans are progressing.

DAVID XU, MD • M. ALI KHAN, MD • ALLEN C. HO, MD

The suprachoroidal space is a potential space spanning from the limbus to the optic nerve, allowing for a depot reservoir where therapeutics can remain in close apposition to their intended target, ie the retina, photoreceptors, or retinal pigment epithelium (RPE), while avoiding exposure of the drug to anterior structures such as the lens, aqueous, and trabecular meshwork.[1] Pharmacokinetic studies have found that agents delivered into the suprachoroidal space diffuse circumferentially from the site of injection, potentially allowing for panretinal therapeutic effect.[2,3]

In recent years, suprachoroidal delivery of ocular therapies has garnered interest and yielded advancements in a number of retinal diseases, owing to the tandem development of therapeutics engineered for suprachoroidal injection (ie, long-lasting corticosteroids[4] and viral vectors[5] with good penetration to the retina) and effective delivery devices for suprachoroidal access. Suprachoroidal injection of triamcinolone acetonide (Xipere, formerly known as CLS-TA; Clearside Biomedical), delivered via a novel transscleral microinjector, was the first suprachoroidal drug to receive FDA approval for the treatment of macular edema due to noninfectious uveitis, in 2021. Adoption of this delivery method for other indications, such as neovascular age-related macular degeneration (AMD),[6] diabetic retinopathy (DR),[7] and ocular melanoma,[8] among others, is anticipated **(Table 1).** Gene therapy and cell-based therapy, delivered via suprachoroidal or suprachoroidal-to-subretinal cannulation, have also matured from preclinical investigation to human trials. In this article, we review the progress made thus far and the state of clinical trial testing for suprachoroidal therapies.

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> In cell delivery, the suprachoroidal technique avoids retinotomy creation, which reduces the potential of reflux of cellular material into the vitreous space.

SUPRACHOROIDAL ACCESS VIA MICRONEEDLE INJECTION

Transscleral microneedle injection is the best studied modality for suprachoroidal drug delivery **(Figure 1).** To date, the SCS Microinjector (Clearside Biomedical) is the suprachoroidal device with the most experience in human studies. The injector incorporates a microneedle with a length of only 900 µm or 1,100 µm, calibrated to reproducibily access the suprachoroidal space without overpenetration.[9] Thus far, the procedure has a well validated safety

Table 1: Human Trials of Suprachoroidal Therapies

THERAPEUTIC NAME(S)	DRUG CLASS	INDICATION	DELIVERY MODALITY	PHASE OF STUDY	CLINICALTRIALS.GOV IDENTIFIER
Triamcinolone acetonide, CLS-TA (Xipere)	Corticosteroid	Macular edema secondary to noninfectious uveitis	Microneedle	FDA approved	
Axitinib, CLS-AX	Tyrosine kinase inhibitor	Neovascular AMD	Microneedle	Phase 1/2a	NCT04626128
Belzupacap sarotalacan, AU-011	Viral nanoparticle	Primary indeterminate lesions and small choroidal melanoma	Microneedle	Phase 1	NCT04417530
RGX-314	AAV8 anti-VEGF Fab	Neovascular AMD, diabetic retinopathy	Microneedle	Phase 2	NCT04567550
Palucorcel, CNTO 2470	Human umbilical tissue derived cells	Geographic atrophy in AMD	Suprachoroidal cannulation	Phase 2	NCT02659098
GT005	AAV2-complement factor I	Geographic atrophy in AMD	Suprachoroidal cannulation	Phase 2	NCT03846193
Human retinal pigment epithelium, Opregen	Human stem-cell derived retinal pigment epithelial cells	Geographic atrophy in AMD	Suprachoroidal cannulation	Phase 1/2a	NCT02286089

profile without major injection-related safety concerns, such as suprachoroidal hemorrhage, endophthalmitis, or retinal detachment following more than approximately 1,200 injections in clinical trials. With the FDA approval of CLS-TA, postmarket surveillance for drug-related and injection-related safety signals will continue as the therapy enters more widespread clinical use.

The injection technique shares similarities with standard intravitreal injection. In-office injection begins with sterilization of the ocular surface followed by insertion of the microneedle in the mid-quadrant of the globe. Pressure is applied to the plunger while the needle is pushed against the globe with enough force to dimple the scleral surface. When the needle tip enters the suprachoroidal space, the user will feel a loss of resistance in the plunger, allowing the plunger to readily advance and deliver the drug. If continued resistance is felt with the 900 µm needle, the longer 1,100 µm needle should then be used.

Small Molecules

The advantage of suprachoroidal injection is closer approximation of the drug depot to the posterior segment compared to periocular injection while reducing cataractogenesis and steroid response glaucoma.[1] CLS-TA is a formulation of triamcinolone acetonide with optimized pharmacokinetic properties for suprachoroidal administration.[10] The phase 3 sham-controlled trial for macular edema secondary to noninfectious uveitis demonstrated the efficacy of CLS-TA, leading to FDA approval in October 2021.[4] In the trial, 47% of patients receiving CLS-TA achieved an improvement in best corrected vision of at least 15 letters compared to 16% in the control arm.

Another small molecule that has been explored is axitinib (CLS-AX, Clearside Biomedical), a tyrosine kinase inhibitor (TKI) currently approved for renal cell carcinoma that exhibits pan-VEGF inhibition, with possible applications for neovascular AMD, DME, and other neovascular disorders. Suprachoroidal axitinib injection was well-tolerated in rabbit models, leading to quantifiable drug levels over the 91-day study period. Currently, the drug has entered phase 1/2a clinical testing for neovascular AMD.[11]

Gene Therapy

Microneedle delivery of gene therapy has also progressed from preclinical to human trials. RGX-314, an AAV8 viral vector delivered anti-VEGF Fab transgene, has entered phase 2 clinical trials for neovascular AMD[6] and DR.[7] These have met with early success. The interim 3-month results of ALTITUDE for DR demonstrated ≥2-step improvement in DR severity score for 33% of patients in the treatment arm compared with 0% in the control arm. The interim 6-month AAVIATE results for neovascular AMD demonstrated approximately 75% reduction of anti-VEGF treatment burden with a mean of 1.2 injections over 6 months in cohort 1 treated at the $2.5x10^{11}$ genome copies/eye dose level. If successful, these therapies may realize the promise of in-office,

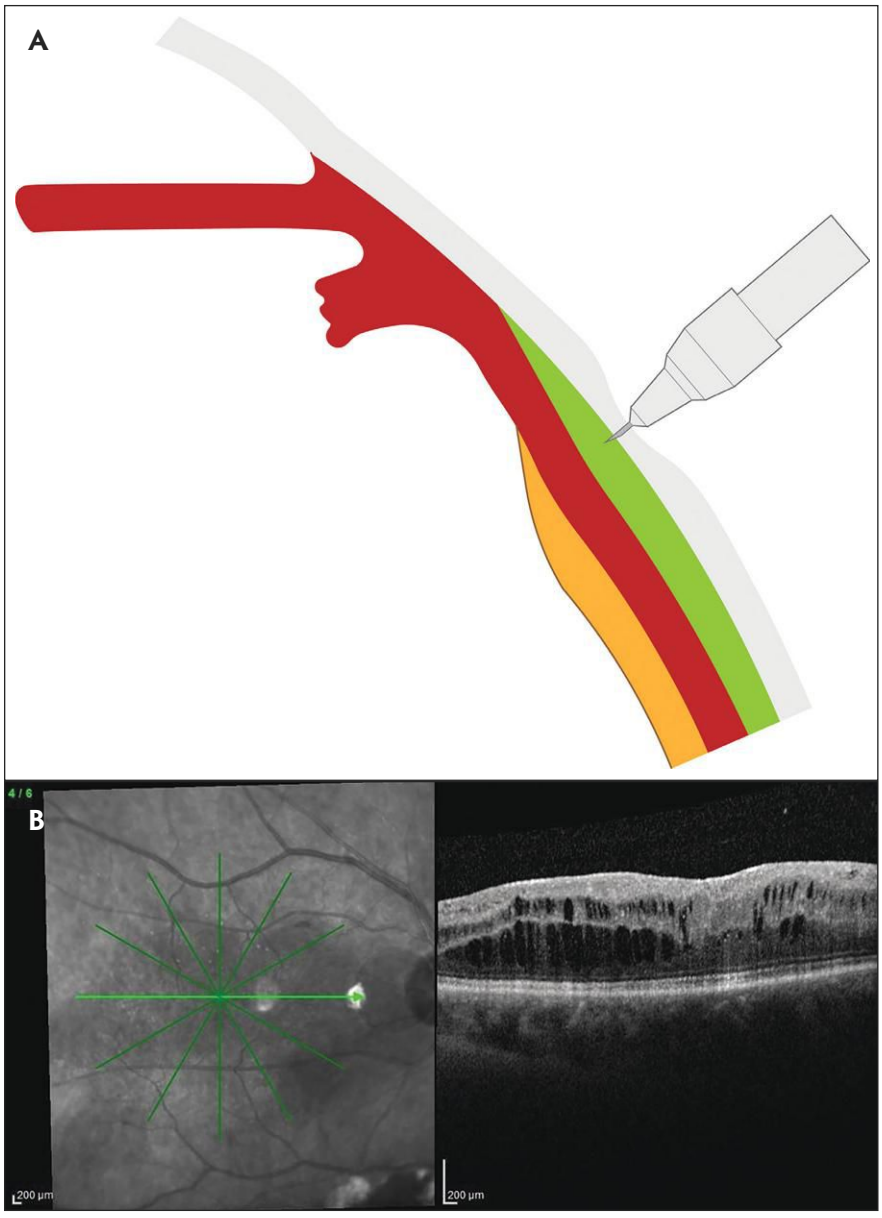

Figure 1. Suprachoroidal microneedle injection with needle length calibrated to reproducibly access the suprachoroidal space and deliver injectate (green) (A). Diffuse macular edema in a 52-year-old female with noninfectious posterior uveitis (B). Currently, injection of triamcinolone acetonide is the only available FDA-approved suprachoroidal therapy.

single-treatment gene therapy for common retinal diseases.

Viral nanoparticle conjugates (VNCs) have also been delivered into the SCS. One such agent is AU-011 (belzupacap sarotalacan; Aura Biosciences), a light-activated VNC modeled on the human papillomavirus, that binds to cells through a modified heparin sulfate proteoglycan moiety. In mouse animal models, injection of AU-011 followed by laser activation led to regression of implanted melanoma cells within the suprachoroidal space. AU-011 entered phase 2 clinical testing for early choroidal melanoma.[8] The drug maintains approximately 5x higher concentrations at the site of the tumor when administered suprachoroidally as compared to intravitreal injection.[12]

Tunneled Suprachoroidal Catheter

Another modality for access of the suprachoroidal space is by introduction of a tunneled suprachoroidal catheter. The catheter runs within the potential space and can be directed to the posterior pole, allowing for more targeted treatment of the macula with gene or cell-based therapies. This technique requires an operative procedure, but unlike pars plana vitrectomy (PPV) with retinotomy creation, suprachoroidal catheterization avoids PPV-related complications such as cataract formation. A number of device iterations have been studied. The most recent Orbit Subretinal Delivery System (Orbit SDS; Gyroscope Therapeutics) features a catheter terminating in an extendable needle that advances from the tip of the catheter and penetrates through the choroid and RPE into the subretinal space, achieving suprachoroidal-to-subretinal injection. A localized conjunctival peritomy and scleral cutdown is performed approximately 5 mm posteriorly to the limbus, exposing the suprachoroidal space where the catheter is inserted. The catheter indents the internal retinal/choroidal surface along its path, enabling visualization with a standard vitrectomy widefield lens (contact or noncontact) and chandelier illumination. The needle at the catheter tip is deployed when the desired location has been reached.

The delivery modality may be suitable for gene therapy or cell therapy delivery. Regarding cell delivery, the suprachoroidal technique avoids retinotomy creation, which reduces the potential of reflux of cellular material into the vitreous space. This both avoids the potential for dose loss and minimizes concerns for epiretinal proliferation, which has been seen with PPV and retinotomy delivery of therapeutic cell suspensions.[13]

The technology was evaluated in phase 1/2 trials of human umbilical tissue–derived cells (palucorcel; Janssen Research and Development) of advanced AMD with geographic atrophy.[14,15] The phase 2b study met its primary safety endpoint and effectively delivered the full cellular

dose ($3.0x10^5$ cells in a 50 µL dosing volume) to the posterior pole in 18 of 21 subjects (86%).[15] Treatment-related adverse events (AEs) occurred in 90% of participants, although all were mild and self-resolving. No specified AEs of interest were noted, including endophthalmitis, retinal detachment, serious subretinal or suprachoroidal hemorrhage, retinal perforation, cell egress, or need for unplanned vitrectomy. At the same time, no specific visual benefit was noted with palucorcel treatment.

> … suprachoroidal cannulation has been employed for GT005 subretinal gene therapy … in phase 1/2 testing (Gyroscope Therapeutics) for geographic atrophy.

The suprachoroidal-to-subretinal delivery system has also been employed in a phase 1/2a clinical trial of transplanted allogeneic RPE cells in advanced dry AMD (Opregen; Lineage Cell Therapeutics). Results of the study are forthcoming. Finally, suprachoroidal cannulation has been employed for GT005 subretinal gene therapy, an AAV viral vector expressing complement factor I, in phase 1/2 testing (Gyroscope Therapeutics) for geographic atrophy.[16,17] The delivery system was split between transvitreal delivery using traditional PPV/retinotomy and the Orbit SDS. Data from the initial cohorts (n=28 patients) demonstrated no dose-related trends in frequency/type of adverse events. There was no evidence of clinically significant drug-induced/immunogenic inflammation. A possible GT005-related event (n=1) was development of neovascular AMD treated with anti-VEGF injections. Eleven of 13 patients with biomarker data demonstrated increased levels of vitreous CFI expression.

CONCLUSION

Use of the suprachoroidal space for delivery of ocular therapies is now currently available, with several trials currently underway for various indications. Trial results and data from "real world" studies will continue to add the breadth of clinical experience utilizing suprachoroidal delivery. **RP**

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Suprachoroidal Drug Delivery in the Treatment of Noninfectious Uveitis

Recent clinical trials have demonstrated promising results.

TOLULOPE FASHINA, MD, MPH • STEVEN YEH, MD

Uveitis, a potentially blinding intraocular inflammatory disease, accounts for up to 10% of visual impairment globally, with approximately one-third of affected patients experiencing vision loss,[1] which can be particularly significant when presentation and diagnosis of uveitis are delayed.

According to the Standardization of Uveitis Nomenclature (SUN) Working Group, uveitis can be classified by anatomic location. Anterior uveitis primarily involves the anterior chamber of the eye, intermediate uveitis primarily involves the vitreous cavity, posterior uveitis primarily affects the retina and/or choroid, and panuveitis can affect all these sites with no site affected predominantly.[2] Although most studies have shown that anterior uveitis is most commonly observed, posterior or panuveitis have been reported to have the worst prognosis, because of their potential to cause irreversible damage to the macula, including macular edema and the potential for optic nerve involvement.[1]

Uveitis can also be classified into infectious or noninfectious categories, because anti-inflammatory therapies are often required for the noninfectious variety but may make infectious uveitis worse if appropriate antimicrobials are not utilized. Examples of infectious uveitis include localized parasitic infections leading to ocular toxoplasmosis or infections that occur as part of a generalized systemic infection due to syphilis or Lyme disease. Noninfectious uveitis (NIU) is, however, commonly immune-mediated and may be associated with systemic diseases, exemplified by pulmonary and ocular involvement in sarcoidosis.[3,4]

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Although infectious forms of uveitis are treated with targeted antimicrobial therapies (eg, antiviral therapy for herpetic retinitis, often in conjunction with anti-inflammatory agents), NIU is treated according to several factors, such as the site of the inflammation and presence or absence of systemic involvement. Corticosteroids are the first line of treatment and are administered locally or via systemic administration. Steroid-sparing immunosuppression may also be required in conjunction with systemic corticosteroid.[5]

Given the side effects associated with systemic corticosteroid (eg, hyperglycemia, mood swings, weight gain) and immunosuppression, local options for corticosteroid administration have been utilized, demonstrating strong efficacy signals; yet the risks of elevated intraocular pressure and cataract need to be considered with local corticosteroid (ie, intravitreal triamcinolone, intravitreal dexamethasone, periocular corticosteroid). Potential limitations associated with drug administration via these routes used in clinical practice have been reviewed and studied in randomized controlled studies.[6-8]

The suprachoroidal space (SCS) is a novel route for drug administration that has been studied extensively in animal models and multiple clinical trials for the treatment of macular edema. It is a potential space between the sclera and choroid that is not immune privileged because of its location outside the blood–retinal barrier.[9] Multiple clinical trials have demonstrated the safety and efficacy of SCS drug delivery.[10]

This review article highlights the SCS as a potential route of drug administration to the eye in the treatment of uveitis. We discuss the benefits of the SCS as a drug delivery route in the treatment of uveitis and summarize

literature findings associated with suprachoroidal drug delivery, particularly related to the recent FDA approval of suprachoroidal triamcinolone acetonide (Xipere; Clearside Biomedical/Bausch + Lomb) for the treatment of macular edema associated with NIU.

POSTERIOR SEGMENT DRUG DELIVERY INNOVATIONS

Intravitreal administration of therapeutic drugs is the most common procedure used to treat NIU and common posterior segment diseases (ie, age-related macular degeneration, diabetic retinopathy, and retinal vein occlusion) in clinical practice. However, other drug delivery routes used previously or under investigation to treat uveitis and posterior segment diseases include topical administration, the sub-Tenon route, subretinal delivery, and, more recently, delivery via the suprachoroidal space. Each of these delivery routes has its benefits and limitations, so retina specialists must consider several factors in choosing a treatment option that may include patients' adherence and drug pharmacokinetics.[11]

Intravitreal Drug Delivery

Intravitreal injection is the most common route of administration in clinical practice for treatment of posterior-segment eye diseases involving direct drug administration into the vitreous cavity. This route has been proven to help enable high and effective drug concentrations into the posterior segment of the eye. However, repeated injections given monthly or bimonthly may result in significant treatment burden, thereby producing a need for alternative innovations that allow more sustained-release systems that would enable a controlled release of therapeutic agents to maintain concentration in the vitreous cavity.[11] Rare complications associated with the intravitreal route of administration include endophthalmitis, elevated intraocular pressure, vitreous detachment, retinal hemorrhage, and cataract.[12] In phakic patients who are receiving intravitreal corticosteroid or sustained-release corticosteroid implants, cataract risk and intraocular pressure elevation that may prompt cataract or filtration surgery, respectively, are important considerations.[13,14]

Suprachoroidal Delivery as an Alternative to Current Techniques

The suprachoroidal space (SCS) is located between the sclera and choroid. Drug delivery into the SCS aids targeting of the posterior segment structures with high levels of medication within chorioretinal structures. Access to the suprachoroidal space has been reported via the use of catheter and hollow microneedles.[15] The SCS is located outside the blood–retinal barrier and can be visualized via advanced techniques of optical coherence tomography.[15] Recent potential benefits of drug delivery via the SCS have been reported, including gene therapy.[16] Yet, given this technique is not widespread in clinical practice, learnings about macular edema associated with NIU, nuances and techniques related to SCS drug administration, and potential for indications beyond uveitis are undergoing further study.

SUPRACHOROIDAL DELIVERY FOR NONINFECTIOUS UVEITIS

Recent multicenter, randomized controlled clinical trials have particularly investigated the use of the suprachoroidal route in the delivery of therapeutic agents for the management of macular edema associated with NIU and have demonstrated strong efficacy signals related to visual acuity and anatomic outcomes by optical coherence tomography. In addition, safety results have been promising, particularly related to rates of intraocular pressure elevation and cataract comparable to sham therapy.[17,18]

In the CLS-TA study group, 47% of patients experienced a significant improvement (≥15 or more EDTRS letters in BCVA) compared to only 16% of patients in the control group (P<.001).

FINDINGS FROM CLINICAL TRIALS

The multicenter, randomized phase 3 PEACHTREE trial investigated the safety and efficacy of suprachoroidally administered triamcinolone acetonide formulation (CLS-TA) by comparing 2 SC-injected CLS-TA (4 mg) to sham treatment at 12 weeks apart in 160 patients with macular edema associated with NIU. Patients were observed for clinical efficacy with a primary outcome of improvement in best-corrected visual acuity (BCVA) and additional clinical outcomes of reduction from baseline in central subfield thickness (CST) and improvements in inflammation over a 24-week period. In the CLS-TA study group, 47% of patients experienced a significant improvement (≥15 or more EDTRS letters in BCVA) compared to only 16% of patients in the control group (P<.001). Mean reductions in CST from baseline were 153 µm in the treatment group vs 18 µm in the control group (P<.001).

Corticosteroid-associated adverse events of elevated

intraocular pressure were however observed in 11.5% of the treatment group and 15.6% of the control group, as well as cataract in 7.3% of the treatment group and 6.3% of the control group.[17] Neither endophthalmitis nor choroidal hemorrhage were described in any patients who were enrolled in PEACHTREE or other recent clinical trials. The US Food and Drug Administration recently approved the triamcinolone acetonide injectable suspension Xipere for the treatment of macular edema in NIU based on the findings of this trial.[19]

The MAGNOLIA trial, an extension of the PEACHTREE trial, investigated the extended 48-week efficacy and safety of suprachoroidal CLS-TA among NIU patients with macular edema. Thirty-three patients (28 CLS-TA group and 5 control group) from the PEACHTREE trial were observed over 24 additional weeks. The median time to rescue therapy was 257 days in the treatment group compared to 55.5 days in the control group, while about 50% of patients in the suprachoroidal CLS-TA treatment group were found to avert additional rescue therapies for up to 9 months following last administration of CLS-TA.[20]

The AZALEA trial investigated the safety of suprachoroidal CLS-TA injections in 38 patients with NIU. Two suprachoroidal injections of CLS-TA (4 mg) each were administered 12 weeks apart. Patients were then observed for adverse events alongside other visual and anatomic outcomes over a 24-week period. Suprachoroidal delivery of CLS-TA was found to be safe and well tolerated in patients with NIU with or without macular edema in the AZALEA trial, with inflammatory signs observed to also improve in a majority of the patients.[21]

CONCLUSIONS AND FUTURE DIRECTIONS

Although intravitreal injections of sight-preserving medications including anti-VEGF agents and corticosteroids remain a mainstay and clinical standard for many posterior-segment diseases, alternative platforms including SCS remain under investigation. Recent clinical trials with SCS injection of triamcinolone acetonide revealed promising results for patients with macular edema associated with NIU, leading to the recent FDA approval of Xipere for this clinical indication in October 2021.

The compartmentalization of medication as well as high levels of therapeutic to the retina and choroid also has the potential to limit exposure of anterior-segment structures to therapeutics and side effects. Other medications are currently under investigation for the SCS for other disease indications, including melanoma, diabetes, and age-related macular degeneration.[22-24] Future understanding of SCS drug delivery will include understanding of posterior-segment diseases that can be targeted by this method of drug delivery, nuances of SCS technique, and durability of medication into the SCS potential space for ophthalmologists and retina specialists implementing this technique into their clinical practice. **RP**

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Current Management of Pediatric Uveitis

Consider these guidelines when facing these challenging patient encounters.

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Although pediatric patients account for only 5% to 30% of the uveitis referrals at tertiary care centers, complications are higher in children than adults.[1-4] In children, uveitis is difficult to diagnose and manage for multiple reasons. Pediatric disease can be asymptomatic and often is more chronic, recurrent, and treatment resistant than in adults.[5] The onset of early disease carries an increased risk of amblyopia and socioeconomic ramifications that accompany visual decline; severe vision loss occurs in approximately 1 in 4 patients.[6] The classification of pathology depends on the main site of ocular involvement and helps develop a differential diagnosis as well as investigations into systemic findings **(Tables 1 and 2).**

ANTERIOR UVEITIS

Anterior uveitis is the most common form of uveitis in children, with rates ranging from 35% to 62%.[5,7,8] The most common causes of anterior uveitis include juvenile rheumatoid arthritis (also known as juvenile idiopathic arthritis or JIA), juvenile onset spondyloarthropathies (JOSPAs), juvenile ankylosing spondylitis, Posner-Schlossmann syndrome (PSS), tubulointerstitial nephritis and uveitis (TINU), familial juvenile systemic granulomatosis (Jabs-Blau syndrome) pediatric sarcoidosis, Fuchs heterochromic iridocyclitis (FHI), poststreptococcal uveitis, trauma, and Beçhet disease.

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Tips for Evaluating Pediatric Patients

- Have a low threshold for scheduling an examination under anesthesia.
- In a history of trauma, evaluate thoroughly for a penetrating globe injury, retained foreign body, or possibility of sympathetic ophthalmia.
- Many pediatric uveitis conditions have systemic manifestations, and a physical examination can help elucidate the diagnosis.
- Early referral to a uveitis specialist is encouraged as chronic undertreated inflammation can result in amblyopia and irreversible complications.

INTERMEDIATE UVEITIS

Intermediate uveitis impacts between 15% and 30% of pediatric uveitis patients. Most cases in children are idiopathic, also known as pars planitis. When evaluating for causes, inflammatory etiologies, such as JIA, sarcoidosis, and multiple sclerosis, as well as infectious causes, such as toxoplasmosis, syphilis, bartonella, tuberculosis, and endophthalmitis should be considered. Additionally, masquerade syndromes, such as leukemia and retinoblastoma, can cause intermediate uveitis-like changes. Intermediate uveitis tends to be asymptomatic more often in children, making it more difficult to detect. Common findings include vitreous cell, snowballs, peripheral retinal vasculitis, and snowbanks. Chronic snowbanks can lead to peripheral neovascularization and vitreous hemorrhage, and vitreous traction overlying these areas can lead to retinal detachment. Dilation in these patients is essential to rule out posterior involvement, which may be clouded by the overlying vitreous cell and haze.

POSTERIOR AND PANUVEITIS

Posterior uveitis and panuveitis are the least common forms of pediatric uveitis. Infectious uveitis is always a concern in the evaluation for posterior uveitis, and should be ruled out, especially when considering local steroid therapy. The most common causes of infectious uveitis include toxoplasmosis and viral etiologies. Common immune causes include pediatric sarcoidosis, Jabs-Blau syndrome, Beçhet disease, systemic lupus erythematosus, antineutrophil cytoplasmic antibody-associated vasculitis, sympathetic ophthalmia, Vogt-Koyanagi-Harada syndrome (VKH), and white dot syndromes.

WORKUP

A complete medical history, ocular history, and familial history are necessary, as well as potential exposures, such as trauma or exposure to infectious agents. As a baseline, most patients are evaluated for 3 common etiologies: sarcoidosis, syphilis, and tuberculosis. In children, angiotensin-converting enzyme levels are not as useful because they tend to be higher in children than adults; however, chest x-ray can be helpful. A full examination can require an examination under anesthesia (EUA) and allows for the collection of intraocular samples. Aqueous samples can detect infections

or masquerade etiologies. The remainder of this article will detail the common etiologies of uveitis in children.

JUVENILE IDIOPATHIC ARTHRITIS

The most common systemic association with anterior uveitis in children is JIA.[9] Chronic, asymptomatic anterior uveitis usually occurs in females with oligoarticular disease, especially when the arthritis sets in before the age of 6, and with positive antinuclear antibodies. In contrast, older males who are HLA-B27 positive tend to develop acute, episodic and symptomatic uveitis. On occasion, patients can also have intermediate findings. Patients generally respond well to topical treatment but can require long-term immunosuppression.

JUVENILE ONSET SPONDYLOARTHROPATHIES

Juvenile onset spondyloarthropathies include reactive arthritis, psoriatic arthritis, inflammatory bowel disease related arthritis, and juvenile ankylosing spondylitis, all of which contribute to anterior uveitis flares in children. A careful review of systems should be done to elucidate systemic symptoms and narrow the diagnosis. Treatment is aimed at both the systemic symptoms and the quiescence of intraocular inflammation.

POSNER-SCHLOSSMANN SYNDROME

Posner-Schlossmann syndrome can also present with episodic increases in intraocular pressure and nongranulomatous anterior-chamber inflammatory episodes. This can be differentiated from other types of anterior inflammation with increased intraocular pressure by its intermittent nature. Other etiologies, such as FHI and viruses tend to have a more chronic presentation.

TUBULOINTERSITITAL NEPHRITIS AND UVEITIS

Another etiology for anterior uveitis is TINU, with the highest incidence of the disease in children and adolescents.[10] Although definite diagnosis requires a renal biopsy, several ancillary tests can help anchor the diagnosis, such as urinalysis with elevated urine beta-2 microglobulin, elevated glucose, protein, and red or white blood cells. Additionally, abnormalities in the serum can show blood urea nitrogen and creatinine levels. In cases of suspected TINU where the labs are not consistent, it may be prudent to retest the patient

Table 1: Most Common Associated Locations of Uveitis by Etiology

Disease	Anterior	Intermediate	Posterior	Panuveitis
ANCA associated vasculitis			X	
Bartonella			X	
Beçhet	X		X	X
Endophthalmitis	X	X	X	X
FHI	X			
Herpesvirdae	X	X	X	X
Jabs-Blau	X		X	X
JAS	X			
JIA	X			
JOSPAs	X			
JXG	X	X		
LCMV				X
Leukemia	X	X		X
Multiple sclerosis		X		
Pars planitis		X		
Poststreptococcal	X		X	
PSS	X			
Retinoblastoma	X	X		X
Retinitis pigmentosa			X	
Sarcoidosis	X	X	X	X
SLE			X	
SO	X		X	X
Syphilis	X	X	X	X
TINU	X	X	X	X
Toxoplasmosis		X	X	X
Trauma	X	X	X	X
Tuberculosis	X	X	X	X
VKH			X	X
WDS			X	X

ANCA, antineutrophil cytoplasmic antibody; FHI, Fuchs heterochromic iridocyclitis; JAS, juvenile ankylosing spondylitis; JIA, juvenile idiopathic arthritis; JOSPAs, juvenile onset spondyloarthropathies; JXG, juvenile xanthogranuloma; LCMV, lymphocytic choriomeningitis virus; PSS, Posner-Schlossmann syndrome; SLE, systemic lupus erythematosus; SO, sympathetic ophthalmia; TINU, tubulointerstitial nephritis and uveitis; VKH, Vogt-Koyanagi-Harada syndrome; WDS, white dot syndrome.

Table 2: Common Systemic Findings Associated With Uveitic Conditions

Feature	Diseases
Joint pain	JIA, JOSPAS, JAS
Skin changes	Jabs-Blau, pediatric sarcoidosis, syphilis, SLE, Ricksetta
Neurologic changes	MS, Beçhets, VKH, APMPPE, congenital viral, toxoplasmosis, LCMV
Trouble breathing	Pediatric sarcoidosis
Systemic illness, fever	TB, poststreptococcal syndrome, endophthalmitis
Oral or genital ulcers	Syphilis, Beçhet, herpes
Trauma	Traumatic iritis, ruptured globe, SO
Iris heterochromia	Trauma, IOFB, FHI, leukemia, JXG
Iris nodules	Many inflammatory causes, trauma, IOFB, FHI, leukemia, JXG, retinoblastoma

APMPPE, acute posterior multifocal placoid pigment epitheliopathy; FHI, Fuchs heterochromic iridocyclitis; IOFB, intraocular foreign body; JAS, juvenile ankylosing spondylitis; JIA, juvenile rheumatoid (idiopathic) arthritis; JOSPAS, juvenile rheumatoid arthritis; JXG, juvenile xanthogranuloma; LCMV, lymphocytic choriomeningitis virus; MS, multiple sclerosis; SLE, systemic lupus erythematosus; SO, sympathetic ophthalmia; TB, tuberculosis; VKH, Vogt-Koyanagi-Harada syndrome.

in a few months, because uveitis can precede development of kidney issues. Tubulointersititial nephritis and uveitis tends to be a predominantly anterior, bilateral, nongranulomatous process, but it has been reported to have granulomatous and/or posterior involvement. Abnormal renal function can occur in other uveitis conditions, including sarcoidosis, and evaluation should include a nephrologist.

JABS-BLAU SYNDROME AND PEDIATRIC SARCOIDOSIS

Familial juvenile systemic granulomatosis (Jabs-Blau syndrome) and pediatric sarcoidosis often present with granulomatous anterior inflammation but can also involve the posterior segment with vitritis, chorioretinitis, retinal vasculitis, and optic neuropathy.[11] In pediatric sarcoidosis, patients younger than 5 tend to have extrapulmonary involvement, such as skin changes and arthritis, while older children often have multisystemic disease and the typical hilar enlargement. Both pediatric sarcoidosis and Jabs-Blau syndrome are associated with *CARD15/NOD2* mutations. The gold standard of diagnosis for sarcoidosis is noncaseating epithelioid granulomas on biopsy.

FUCHS HETEROCHROMIC IRIDOCYCLITIS

Other etiologies for infectious uveitis include FHI, which has been linked to the rubella virus. Fuchs heterochromic iridocyclitis may cause as many as 7% of the anterior uveitis cases in North America, and onset is often in young adulthood. A strong suspicion for this diagnosis is important in patients who present with unilateral anterior inflammation, elevated intraocular pressure, and stellate keratic precipitates throughout the cornea, especially with a lack of posterior synechiae. Posterior subcapsular cataracts are also common with this disease. When treating FHI, it is important to remember that topical steroids do not usually help the inflammation, but management of the glaucoma is crucial.

POSTSTREPTOCOCCAL SYNDROME

In children with a history of streptococcal pharyngitis, poststreptococcal syndrome uveitis is a possibility, and this can have anterior and posterior findings, such as granulomatous or nongranulomatous anterior uveitis and phlebitis. Antistreptolysin O (ASO) titers can be elevated for up to 6 weeks following infection.[12] Treatment involves monitoring of the ASO titers and treatment of the streptococcal infection.

TRAUMA

Trauma is a cause of uveitis, with one series attributing almost 5% of cases of uveitis at a referral center to a traumatic incident.[13] Traumatic iritis commonly responds to topical steroids; however, in cases of trauma, penetrating ocular injury and intraocular foreign body should be ruled out with appropriate imaging and EUA as necessary **(Figure 1).**

BEÇHET DISEASE

Beçhet disease most commonly presents with posterior findings, such as retinal vasculitis, but severe anterior uveitis with a hypopyon can occur in unison. Beçhet disease is of utmost importance to recognize, as extraocular manifestations include devastating complications, such as cerebral lesions. Involvement in the pediatric patient is rare, with an average of 5% of cases occurring in children.[14] Systemic findings also include ulcers of the mouth and genitals and skin pathergy.

SYSTEMIC LUPUS ERYTHEMATOSUS

Systemic lupus erythematosus is a multisystemic disease that can occur in any age group, but in children, the disease tends to be aggressive and can have atypical presentations. Along with the more common retinal vasculitis picture, optic nerve involvement and retinal and choroidal changes have been reported.[15]

ANTINEUTROPHIL CYTOPLASMIC ANTIBODY ASSOCIATED VASCULITIDES

Antineutrophil cytoplasmic antibody-associated vasculitides mainly impact small and medium-sized vessels. Etiologies in this group include granulomatosis with polyangiitis, microscopic polyangiitis, eosinophilic granulomatosis with polyangiitis, and polyarteritis nodosa (PAN). These diseases rarely impact children, and of

these, granulomatosis with polyangiitis is the most common, with orbital involvement, episcleritis and scleritis more prevalent than the posterior findings of optic neuropathy and retinal vasculitis.

SYMPATHETIC OPHTHALMIA

Sympathetic ophthalmia (SO) is linked to a T-cell response to antigens within the retina and uvea, often in the setting of penetrating ocular trauma or ocular surgery. The exposure of the uveal antigens to the immune system generates inflammation in both eyes. Patients can present with anterior inflammation, posterior inflammation, or panuveitis. Debate exists on the management of the injured eye. Initially, practice patterns dictated that if an eye has no light perception vision, it should be removed within 2 weeks. However, there are reports of inflammation impacting the contralateral eye in shorter periods and inflammation that occurs even after the injured eye was enucleated. Long-term management usually requires immunosuppression.

WHITE DOT SYNDROMES

The conglomerate of white dot syndromes includes inflammatory disorders of the outer retina, retinal pigment epithelium, and choroid and is comprised of multiple evanescent white dot syndrome, acute posterior multifocal placoid pigment epitheliopathy (APMPPE), multifocal choroiditis (MFC) with or without panuveitis, punctate inner choroiditis (PIC) and acute zonal occult outer retinopathy. White dot syndromes generally present similarly in adults and children. Multiple evanescent white dot syndrome produces a granular macular appearance with tiny subretinal white or yellow lesions, while APMPPE typically has larger lesions that block early on fluorescein angiography. As with adults, neurologic symptoms can accompany the diagnosis of APMPPE and a neurological review of system is essential. MFC and PIC both have distinct subretinal lesions; MFC has vitritis and PIC does not. Acute zonal occult outer retinopathy tends to impact young women with an enlarged blind spot and ellipsoid zone changes **(Figure 3).** Autoflouresence can reveal zonal areas of hyperautofluorescence and hypoautoflouresnce. Patients should be monitored for the development of choroidal neovascular membranes in any of these etiologies.

VOGT-KOYANAGI-HARADA SYNDROME

Like SO, VKH is a T-cell mediated response to retinal and uveal antigens. It occurs more often in Asians, Hispanics, and Native Americans. Systemic findings include central nervous system changes, including aseptic meningitis, and cutaneous manifestations, such as vitiligo and poliosis. Pediatric cases comprise up to 15% of VKH cases and often the disease is more aggressive in children than in adults **(Figure 2).**[16]

INFECTIOUS CAUSES

Depending on the geographic location, infectious uveitis in children accounts for up to 30% of the of pediatric uveitis cases and is imperative

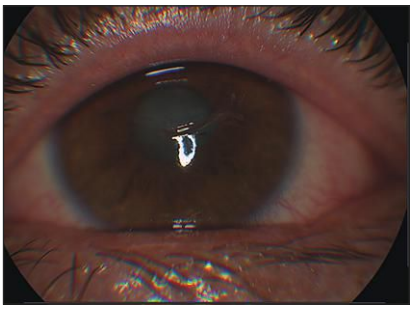

Figure 1. A 16-year-old patient referred for traumatic iritis. Examination the cornea shows a full-thickness corneal wound that has sealed, with 4+ cell and no view of the lens. Computed tomography showed a retained intraocular foreign body, and the patient underwent a pars plana vitrectomy with foreign body removal and lensectomy.

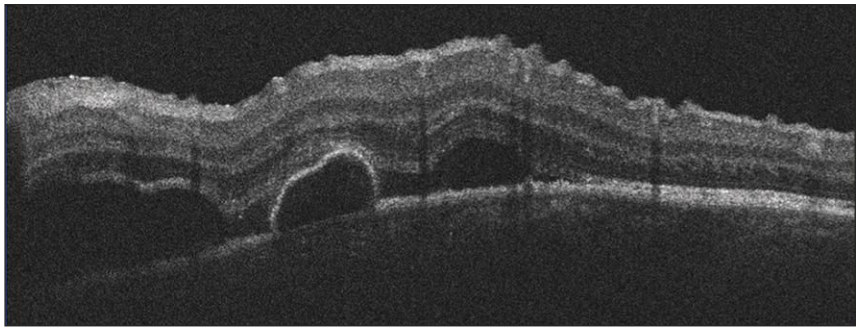

Figure 2. A young male presenting with septae on optical coherence tomography, consistent with Vogt-Koyanagi-Harada syndrome, that improved with oral steroid treatment.

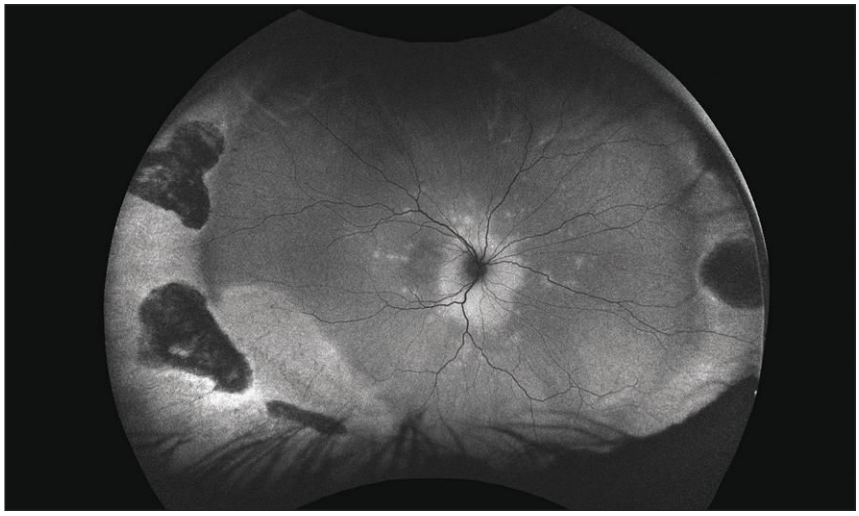

Figure 3. A 17-year-old female with a history of retinal detachment previously repaired with scleral buckle presents with acute zonal occult outer retinopathy-like changes seen on autofluorescence.

to rule out before starting high-dose steroids.[8,17] Pediatric infectious uveitis can be congenital or acquired, and the most common pathogens are toxoplasmosis and viral etiologies.[18] When considering viral etiologies, the Herpesviridae family is the most common cause, and these include human herpes simplex virus, varicella-zoster virus, cytomegalovirus, human herpes virus, and Epstein-Barr virus.

TOXOPLASMOSIS

Toxoplasmosis can present with a variety of inflammatory findings ranging from anterior uveitis to panueveitis. Especially in cases of suspected congenital infection, a systemic workup is warranted, because the organisms can migrate to neural tissue and rupture. Congenital toxoplasmosis can be asymptomatic to severe, with microphthalmia, hydrocephalus, and developmental issues. Acquired toxoplasmosis is more common than congenital. Typically, reactivation of the infection occurs on the margins of the old chorioretinal scar with overlying inflammation and possible vasculitis. Serum antibody testing for toxoplasmosis as well as ocular PCR can confirm the diagnosis. Multiple treatment regimens aimed at the organism exist.

HERPESVIRIDAE

Common findings with viral infections include ocular hypertension, corneal dendrites, keratic precipitates that do not respect Arlt's triangle, iritis, and iris atrophy. A dilated eye examination is crucial to rule out retinitis posteriorly, which can sometimes mimic toxoplasmosis. Congenital infections also pose devastating systemic implications. In particular, cytomegalovirus, the most common intrauterine infection, can result in intrauterine growth restriction, sensoneural hearing loss, and microcephaly.[19] Congenital varicella-zoster virus can result in cerebral atrophy, seizures, and growth deformities, along with striking white centered chorioretinal scars with a black ring.[20] Congenital herpes simplex virus infections can present in 3 ways: (1) with disseminated infection, (2) encephalitis, or (3) skin, eye, and mouth infection. In skin, eye, and mouth infection, conjunctivitis may be the only finding, or posterior involvement can include retinitis, or with punctate white and yellow lesions in the posterior pole along with hemorrhage, or panuveitis.[20] An EUA may be necessary in these cases to rule out posterior involvement as well as aid in obtaining intraocular samples to test for viral PCR. Treatment includes systemic and intraocular antivirals, along with cautious use of topical steroids, especially in cases of corneal dendritic involvement.

LYMPHOCYTIC CHORIOMENINGITIS VIRUS

Congenital lymphocytic choriomeningitis virus can result in defects in the central nervous system, developmental issues, and chorioretinal lesions that appear similar to toxoplasmosis. Treatment is usually supportive.

SYPHILIS

With rates of syphilis increasing, the rates of congenital syphilis are also expected to rise. Congenital findings include rhinitis, pneumonia, desquamating skin rash, and deafness, along with any variation of intraocular inflammation including chorioretinitis, retinitis, or retinal vasculitis. Congenital syphilis can also produce a "salt and pepper fundus" in young children. Acquired syphilis also presents in a myriad of ways, but placoid chorioretinitis should raise concern for the disease. Evaluation involves treponemal and nontreponemal testing, and treatment should adhere to the guidelines for central nervous system syphilis.

MYCOBACTERIUM TUBERCULOSIS

Like syphilis, tuberculosis can present in a variety of ways. In particular, granulomatous uveitis, serpigneous like changes, or choroidal granulomas raise the concern for the disease, and quantiferon testing can confirm the diagnosis, along with chest imaging. Antituberculosis therapy should be initiated with infectious disease.

BARTONELLA HENSELAE

While most classically associated with a neuroretinitis, Bartonella henselae also produces a retinitis and choroiditis, along with vascular occlusions. The diagnosis is confirmed by antibody testing, and treatment involves antibiotics such as doxycycline, erythromycin, or azithromycin.[21]

RICKETTSIA

Rickettsia can cause profound systemic effects, including fevers, rashes, and flu-like symptoms. Evaluating for recent travel or outdoor activities which may predispose to tick bites is essential in these patients. Patients can develop a multitude of posterior uveitis findings, including retinal vasculitis, retinal lesions, and choroiditis. Antibiotics targeting the bacteria, including doxyclycine or macrolides, are typically used.[22]

TOXOCARA

Classically, the lesions in toxocara are associated with peripheral or central granulomas surrounded by retinal traction and pigmentary changes. Rarely, the patient can have diffuse inflammation without a specific lesion. Serologic testing is of low utility in these patients. Antihelminthic treatment can be helpful, and surgical intervention is necessary in the cases of tractional retinal detachments.[23]

ENDOPHTHALMITIS

Exogenous endophthalmitis is always a risk of intraocular procedures, while endogenous endophthalmitis usually occurs in the setting of a systemically ill patient. A careful medical and surgical history examination should be done to assess for risk factors. Treatment is aimed at irradiation of systemic risk factors and treating the intraocular pathogens.

DIFFUSE UNILATERAL SUBACUTE NEURORETINITIS

Subretinal nematodes, such as

Bayliascaris procyonis, can cause widespread retinal degeneration and atrophy following areas of outer retinal and choroidal multifocal lesions, vitritis, and optic disc edema followed by pallor. Ideally, identification of the worm on fundoscopy and treating with photocoagulation is the preferred treatment, but albendazole can also be used.

MASQUERADE

Masquerade syndromes can often muddy the differential diagnosis for a child, particularly in the cases where examination is difficult or limited in the clinic. As with all cases of uveitis, a careful medical history, family history, and dilated eye examination are necessary to help make the diagnosis.

LEUKEMIA

Leukemia is the most common malignancy of childhood, and anterior inflammation most often occurs in the setting of acute lymphoblastic leukemia. Patients can have either unilateral or bilateral anterior chamber involvement, with a pseudohypopyon (usually creamy white in color with shaggy material that does not neatly settle or has a lumpy appearance). Patients can also present with a hyphema. These can initially respond to topical steroids but will fail to resolve the collection completely. Iris infiltration can result in iris nodules, heterochromia, or elevated intraocular pressure from trabecular meshwork invasion.[24] An anterior chamber collection with cytologic evaluation can help make the diagnosis with the help of oncology for further management.

RETINOBLASTOMA

Retinoblastoma remains the most common intraocular malignancy of childhood, usually impacting children under the age of 5 years. Anterior chamber inflammation can either occur in setting of tumor necrosis or from circulating malignant cells. Uveitis has been reported in up to 40% of patients with retinoblastoma, and iris infiltration has also been noted.[25] The enrollment of an ocular oncologist and systemic oncologist are mandatory in the management of these patients.

JUVENILE XANTHOGRANULOMA

Juvenile xanthogranuloma is primarily a cutaneous disorder, but involvement of ocular structures can include the uvea, cornea, conjunctiva, retina, and optic nerve. Patients with juvenile xanthogranuloma are usually under the age of 2 years. Anterior-chamber involvement can involve circulating white blood cells, hyphema, iris nodules, heterochromia, and/or elevated intraocular pressure from invasion of the angle.[26] Aqueous samples can aid in the diagnosis, with histology showing various inflammatory cells, foamy histocytes, and staining with Oil Red O for fatty deposits.

RETINITIS PIGMENTOSA

Retinitis pigmentosa has an overlapping clinical picture with chronic uveitis, including posterior subscapular cataracts, mild vitreous cell, cystoid macular edema, and peripheral perivascular pigmentary changes. Electroretinogram can help elucidate the diagnosis, and fluorescein angiography should not have an inflammatory pattern of leakage.

SUMMARY

The differential for pediatric uveitis is large. However, careful attention to location, onset, exposures, and systemic manifestations can help narrow the diagnosis. **RP**

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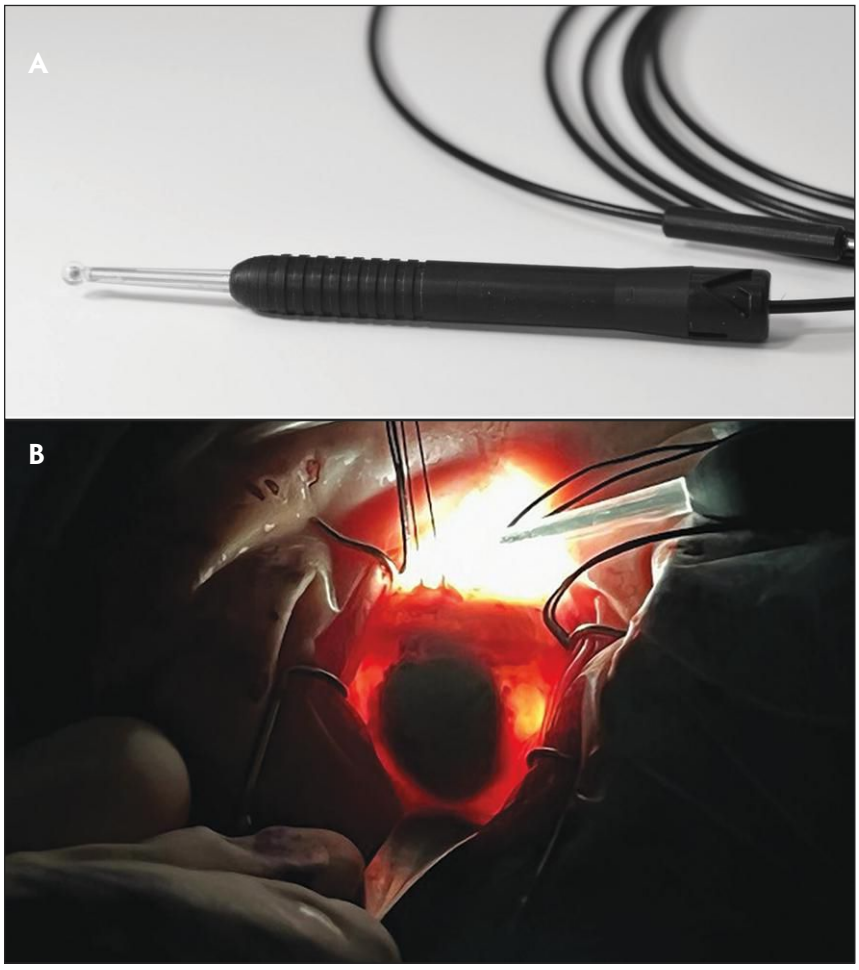
BY KAREN APPOLD, CONTRIBUTING WRITER

The Next Generation of Vitrectomy Lighting

Transilluminating depressor offers brighter visualization.

Vortex Surgical's TID Pharos Illuminated Depressor is the first standalone transilluminator that can be used across all existing vitrectomy machine platforms without requiring a skilled assistant. The product is the second generation of the company's line of transillumination products, which includes the first-generation Todorich Illuminated Depressor (TID) launched in 2019.

"The TID Pharos design was the next step in developing our transillumination family of products," says Bob Neu, vice president of development and integration at Vortex Surgical.



The TID Pharos handpiece (A) and TID Pharos illuminating an ocular tumor (B). *Images courtesy Vortex Surgical*

Bozho Todorich, MD, PhD, who developed both the first-generation and second-generation depressor transilluminators along with Vortex Surgical, says the TID Pharos allows for better visualization during depression than its predecessor. "It was born out of the market's need for better visualization, brighter illumination, a more ergonomic design, and ubiquitous adaptability, while promoting a surgeon's independence," says Dr. Todorich, a vitreoretinal surgeon at Lehigh Eye Specialists in Allentown, Pennsylvania.

Although modern vitrectomy machines have automated most critical steps, many vitreoretinal specialists continue to depend on skilled assistants for scleral depression during peripheral vitrectomy. "Vortex depressor-transilluminators eliminate that problem by giving surgeons full and independent control of this step also," Dr. Todorich says.

The new depressor's name is a nod to the Pharos of Alexandria, a famous lighthouse and one of the seven wonders of the ancient world. "The TID Pharos provides illumination in a sideways manner, mimicking a lighthouse's ability to light the path at a 90-degree angle," Neu explains.

WHAT IT CAN DO

The TID Pharos allows surgeons to simultaneously depress and perform unassisted transillumination of the peripheral eye wall while shaving the vitreous base. One hand holds the vitrector and the other depresses

and transilluminates. "This technique is most applicable in cases where thorough peripheral vitrectomy is paramount, such as a rhegmatogenous retinal detachment repair," Dr. Todorich says.

Transillumination can also be used to localize tumors for planning of radiation seed placement and to identify and remove retained lens fragments, remove sequestered peripheral vitreous hemorrhages, and enhance vitreous base visualization during scleral fixated IOL cases. The first-generation device had a cap-over design that could be fitted over a vitrectomy light pipe, providing longitudinal or coaxial illumination. Its main limitation was the output of light intensity limited by the light pipe, Dr. Todorich says.

The TID Pharos's "side fire illumination" technology, which has a US patent pending, allows surgeons to have a brighter view and produces less glare when compared to other cap-over designs where the illumination is directed out the tip of the device, Neu says. The device's conventional ballpoint depressor tip is made of transparent acrylic, providing surgeons with an ergonomic but sturdy and effective depressor tip that glides seamlessly on the scleral surface.

The TID Pharos is a standalone, disposable, complete transilluminator that can connect directly to Alcon, Bausch + Lomb, and DORC Eva vitrectomy machines. "This is advantageous compared to other cap-over designs because it allows for the transilluminator and the regular endoilluminator to be available at all times during a surgery," Neu says.

Surgeons can toggle between the light pipe and transilluminator seamlessly without any down time to put the cap on and off. The transilluminator performs well with both conventional microscopes as well as digital viewing, such as Alcon's Ngenuity.

According to Dr. Todorich, "The novel platform allows vitreoretinal surgeons to be fully independent. For those of us in private practice who don't have consistent access to skilled staff, residents, or fellows, this is a game changer because everything else is automated and at a surgeon's fingertips and toe tips."

"The novel platform allows vitreoretinal surgeons to be fully independent."

EASE OF USE

The TID Pharos handle was designed to fit comfortably in a surgeon's hand. "The device's illumination fiber isn't very heavy and doesn't weigh down or impede a surgeon's movement," Neu says. "By being able to directly connect the depressor into a vitrectomy machine, it can be available at any point in a case."

Along these lines, Dr. Todorich says the depressor feels light — just like existing conventional depressors. It doesn't require additional skills, plugs into the machine like any other lighted instrument, and takes advantage of a surgeon's existing skill set while adding to the surgical experience and armamentarium. The learning curve is quick.

The only other way to perform independent depressed vitrectomy is to use a chandelier light. However, Dr. Todorich says, chandelier illumination is more expensive and is not uniform, with areas of glare and dark illumination, and it is static. This can compromise view and increase chance of iatrogenic retinal breaks.

Vortex Surgical's TID and TID Pharos overcame some of these limitations because surgeons can dynamically move the instrument to areas where they're performing a vitrectomy. They can adjust the lighting to maximize view and highlight vitreous and retina to improve visualization.

"Instead of broad endoillumination, TID Pharos provides focused, task-specific illumination," says Dr. Todorich. "This takes some getting used to, but once mastered, offers surgeons an unprecedented level of independence, control, and visualization." Transilluminators aren't intended to replace conventional endoillumination, but to complement and enhance surgeon's experience for specific parts of a case.

HOW PATIENTS BENEFIT

By allowing surgeons to depress while looking for breaks or tears at the end of a case, the TID Pharos can improve patient outcomes, Neu says.

"If you don't have access to an assistant or chandelier, the alternative is to not shave the vitreous base," Dr. Todorich says. "However, if you're doing a primary vitrectomy for a retinal detachment repair and you don't perform an adequate peripheral vitrectomy, I think this decreases the surgical success rate of primary retinal detachment repair. Furthermore, less reliance on assistants may reduce the rate of iatrogenic breaks." **RP**

UVEITIS

Study: Phase 2b Pivotal Study of Izokibep in Non-infectious, Intermediate-, Posterior- or Pan-uveitis
Clinicaltrials.gov Identifier: NCT05384249
Sponsor: ACELYRIN Inc.
Purpose: Izokibep is a small protein molecule that acts as a selective, potent inhibitor of interleukin-17A, to which it binds with high affinity. Izokibep has been investigated in non-clinical and clinical studies including healthy subjects and patients with psoriasis and psoriatic arthritis and is currently being studied in uveitis, axial spondyloarthritis and hidradenitis suppurativa. This study investigates izokibep in subjects with active non-infectious, intermediate-, posterior- or pan-uveitis requiring high-dose steroids.
Design: Randomized, parallel assignment, double masking
Number of Patients: 120
Inclusion Criteria: Subject or legally authorized representative has provided signed informed consent including consenting to comply with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol. 18 years to 75 years of age. Type of Subject and Disease Characteristics: Subject is diagnosed with non-infectious intermediate-, posterior- or pan-uveitis. Active disease defined by the presence of at least 1 of the following criteria in at least 1 eye despite treatment with stable doses of corticosteroids for at least 2 weeks prior to day 1: Active, inflammatory, chorioretinal and/or inflammatory retinal vascular lesion by dilated indirect ophthalmoscopy, fundus photography, fluorescein angiography (FA), and Spectral-Domain Optical Coherence Tomography (SD-OCT) to determine whether a lesion is active or inactive (the central reading center assessment using FA, fundus photography and/or SD-OCT is required to confirm eligibility prior to day 1). ≥ 2+ vitreous haze (National Eye Institute [NEI]/Standardization of Uveitis Nomenclature [SUN] criteria) by digital indirect ophthalmoscope and fundus photography (the central reading center assessment using fundus photography is required to confirm eligibility prior to day 1). Currently receiving treatment with oral corticosteroids (≥ 7.5 mg/day to ≤ 40 mg/day oral prednisone/prednisolone or corticosteroid equivalent) at a stable dose for at least 2 weeks prior to day 1.
Exclusion Criteria: Disease-related medical conditions: Subject with isolated anterior uveitis. Subject with serpiginous choroidopathy. Subject with confirmed or suspected infectious uveitis. Subject with corneal or lens opacity that precludes visualization of the fundus or that likely requires cataract surgery during the duration of the study. Subject with intraocular pressure of ≥ 25 mmHg while on ≥ 2 glaucoma medications or evidence of glaucomatous optic nerve injury. Subject with severe vitreous haze that precludes visualization of the fundus prior to first dose of study intervention. Other protocol defined Inclusion/Exclusion criteria may apply.
Information: clinicaltrials@acelyrin.com

Study: A Trial of the Efficacy and Safety Trial of ABY-035 in the Treatment and Prevention of Relapse/Recurrence of Non-anterior Uveitis (LINNAEA)
Clinicaltrials.gov Identifier: NCT04706741
Sponsor: Affibody
Purpose: This is a multinational, multicenter, phase 2 proof-of-concept trial to explore the efficacy and safety of ABY-035 in treating and preventing relapse/recurrence of disease activity in patients with non-Infectious Intermediate, Posterior, Pan-Uveitis with significant BL disease activity despite treatment with stable doses of corticosteroids (≥7 to ≤40 mg/day oral prednisolon or equivalent).
Design: Randomized, parallel assignment
Number of Patients: 110
Inclusion Criteria: ≥18 years of age at SCR. Previously documented medical history with diagnosed unilateral or bilateral NIIPPU. Active disease at BL defined by the presence of at least 1 of the following criteria in at least one eye despite treatment with stable doses of corticosteroids for at least 2 weeks: Active, inflammatory, chorioretinal and/or inflammatory retinal vascular lesion by Dilated Indirect Ophthalmoscopy (DIO) and Fundus Photography to determine whether a lesion is active or inactive (the central reader's assessment using Fundus Photography is required to confirm eligibility). ≥2+ vitreous haze (NEI/SUN criteria) by DIO and Fundus Photography (the central reader's assessment using Fundus Photography is required to confirm eligibility). On treatment with oral corticosteroids (≥7 to ≤40 mg/day oral prednisolon or equivalent) at a stable dose for at least 2 weeks before BL.
Exclusion Criteria: Subject with isolated anterior uveitis. Subject with Occlusive Behçet's disease, Acute Posterior Multifocal Placoid Pigment Epitheliopathy, Acute Posterior Pigment Epithelitis, Multiple Evanescent White Dot Syndrome, Punctate Inner Choroiditis or serpiginous choroidopathy. Subject with confirmed or suspected infectious uveitis, including but not limited to infectious uveitis due to TB, syphilis, cytomegalovirus, Lyme disease, toxoplasmosis, Human T-Lymphotropic Virus Type 1 infection, Whipple's disease, herpes zoster virus, and herpes simplex virus. Subject with corneal or lens opacity that precludes visualization of the fundus or that likely requires cataract surgery during the duration of the trial. Planned (elective) eye surgery within 80 weeks after BL. Additional exclusion criteria at www.clinicaltrials.org.
Information: linnaea@affibody.se

Study: Safety and Efficacy of an Injectable Fluocinolone Acetonide Intravitreal Insert (FAI)
Clinicaltrials.gov Identifier: NCT05070728
Sponsor: EyePoint Pharmaceuticals, Inc.
Purpose: A study to evaluate the safety and efficacy of an FAI insert for the management of subjects with non-infectious uveitis affecting the posterior segment of the eye.
Design: Randomized, parallel assignment, double masking
Number of Patients: 60
Inclusion Criteria: Male or non-pregnant female at least 18 years of age at time of consent. One or both eyes having a history of recurrent non-infectious uveitis affecting the posterior segment of the eye (intermediate, posterior, or panuveitis) with or without anterior uveitis > 1 year duration. During the 52 weeks prior to enrollment (Day 1), the study eye has either received treatment systemic corticosteroid or other systemic therapies given for at least 12 weeks, and/or at least 2 intra- or periocular injections of corticosteroid for management of uveitis OR the study eye has experienced recurrence recurrences of uveitis at least 2 separate times requiring systemic, intra- or peri-ocular injection of corticosteroid. Subject is not planning to undergo elective ocular surgery during the study. Subject has ability to understand and sign the Informed Consent Form (ICF). Willingness and ability to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures. Other protocol-specified inclusion criteria may apply.
Exclusion Criteria: History of posterior uveitis only that is not accompanied by vitritis or macular edema. History of iritis only associated with no vitreous cells, anterior chamber cells, or vitreous haze at Day 1. Uveitis with infectious etiology. Vitreous hemorrhage. Intraocular inflammation associated with a condition other than noninfectious uveitis (eg, intraocular lymphoma). Uveitis limited to the anterior segment, ie, anterior uveitis only. Ocular malignancy in either eye, including choroidal melanoma. Previous viral retinitis. Requirement for chronic systemic or inhaled corticosteroid therapy (>15 mg prednisone daily) or chronic systemic immunosuppressive therapy. Additional exclusion criteria at www.clinicaltrials.org.
Information: dpaggiarino@eyepointpharma.com

For full listings including exclusion and inclusion criteria, please visit this issue at www.retinalphysician.com.

CLINICAL TRIAL UPDATE

Study: Systemic and Topical Antivirals for Control of Cytomegalovirus Anterior Uveitis: Treatment Outcomes (STACCATO)
Clinicaltrials.gov Identifier: NCT03586284
Sponsor: University of California, San Francisco
Purpose: A double-masked randomized controlled clinical trial comparing the efficacy of oral valganciclovir, topical ganciclovir 2%, and placebo for the treatment of PCR-proven CMV anterior uveitis. This pilot study will provide valuable information concerning the treatment of CMV anterior uveitis with oral and topical medications, including effective concentrations and side-effect profile. The information obtained from this study will help inform future larger clinical trials in CMV anterior uveitis.
Design: Randomized, parallel assignment, quadruple masking
Number of Patients: 99
Inclusion Criteria: Clinical impression consistent with CMV anterior uveitis. Directed PCR positive for CMV OR previous PCR-proven CMV anterior uveitis. Willingness to use an acceptable method of contraception during the study period (ie pharmacologic, devices, barrier methods) or abstinence.
Exclusion Criteria: Patients <18 years of age. Intermediate or posterior inflammation (involvement of vitreous, choroid, or retina). Received antiviral therapy <14 days prior to enrollment. Received periocular or intraocular corticosteroid injection <8 weeks prior to enrollment. Currently taking oral corticosteroids. Immunocompromised (primary or secondary immunosuppressive disorders). Prior immunosuppressive therapy in the past 6 months. Directed PCR negative for CMV. Additional exclusion criteria at www.clinicaltrials.org.
Information: john.gonzales@ucsf.edu

Study: Tofacitinib for Inflammatory Eye Disease
Clinicaltrials.gov Identifier: NCT03580343
Sponsor: Washington University School of Medicine
Purpose: Non-infectious inflammatory eye disease, such as uveitis and scleritis, is a chronic, autoimmune process that leads to vision loss. While steroids are effective in the short term, the side-effect profile of chronic steroid use necessitates the identification of effective steroid-sparing therapies. Tofacitinib is a small molecule that inhibits the signaling pathways of multiple inflammatory cytokines. The investigators plan to evaluate whether tofacitinib may have efficacy for patients with uveitis and/or scleritis.
Design: Single group, no masking
Number of Patients: 5
Inclusion Criteria: Diagnosis of uveitis; a clinical response to steroids; active disease requiring at least 10 mg of prednisone daily (or steroid equivalent).
Exclusion Criteria: Suspected or confirmed ocular infection; chronic or recurring infections, such as HIV; renal insufficiency that would preclude safe administration of tofacitinib.
Information: laceyfeigl@wustl.edu

Study: Adalimumab vs Conventional Immunosuppression for Uveitis Trial (ADVISE)
Clinicaltrials.gov Identifier: NCT03828019
Sponsor: JHSPH Center for Clinical Trials
Purpose: Based upon preliminary data, adalimumab, a fully-human, anti-TNF-α monoclonal antibody, now US FDA-approved for uveitis treatment, may be a superior corticosteroid-sparing agent than conventional immunosuppressive drugs. The ADVISE Trial is multicenter randomized, parallel-treatment, comparative effectiveness trial comparing adalimumab to conventional (small molecule) immunosuppression for corticosteroid spring in the treatment of non-infectious, intermediate, posterior, and panuveitides.
Design: Randomized, parallel assignment, no masking
Number of Patients: 222
Inclusion Criteria: Age 13 years or older; active or recently active (≤60 days) non-infectious, intermediate, posterior, or panuveitis; prednisone indication meets one of the following: a. Active uveitis requiring one of the following i. Initiation of prednisone at dose greater than 7.5 mg/day ii. Increasing prednisone dose to greater than 7.5 mg/day iii. Currently receiving dose greater than 7.5 mg/day; b. Inactive uveitis on current dose greater 7.5 mg/day. Initiation or addition of an immunosuppressive drug (ie, a conventional immunosuppressive drug or adalimumab) is indicated. If currently receiving a conventional immunosuppressive drug, the drug and dose have been stable for at least 30 days. Patient able and willing to self-administer subcutaneous injections or have a qualified person available to administer subcutaneous injections. If posterior segment disease is present, ability to assess activity in at least 1 eye with uveitis. Visual acuity of light perception or better in at least 1 eye with uveitis.
Exclusion Criteria: Active tuberculosis or untreated latent tuberculosis (eg, positive interferon-γ release assay [IGRA] test, such as Quantiferon-gold). Untreated active hepatitis B or C infection. Behçet disease. Multiple sclerosis. For patients with intermediate uveitis, abnormal magnetic resonance imaging (MRI) of the brain consistent with demyelinating disease. Use of anti-TNF monoclonal antibody therapy within past 60 days. History of adalimumab intolerance or ineffectiveness. Current treatment with an alkylating agent. Current treatment with more than 1 immunosuppressive drug, not including oral corticosteroids. Shorter-acting regional corticosteroids administered within the past 30 days in any eye(s) with uveitis. Long-acting ocular corticosteroid implants, ie, fluocinolone acetonide implant (eg, Retisert, Yutiq, Iluvien) placed within past 3 years unless uveitis is active in all eye(s) with an implant. Systemic disease that is sufficiently active such that it dictates therapy with systemic corticosteroids or immunosuppressive agents at the time of enrollment. Additional exclusion criteria at www.clinicaltrials.org.
Information: jholbro1@jhu.edu, esugar2@jhu.edu

Study: OCT Technology Development to Assess Ocular Integrity and Characterize Ocular Integrity and Intraocular Scatterers
Clinicaltrials.gov Identifier: NCT03531853
Sponsor: Duke University
Purpose: The purpose of this study is to develop and demonstrate new technologies that will enable a non-contact, compact eye imaging system based on OCT to assist an early responder in acute care settings (like an emergency room) to help assess eye trauma and inflammation (swelling inside the eye).
Design: Single group, open label
Number of Patients: 75
Inclusion Criteria: Pre-clinical: employees or students (over the age of 18) of the Duke Eye Center or Biomedical Engineering willing to be imaged with OCT system; pilot (ER): patients (over the age of 18) presenting emergently to the Duke Emergency room with traumatic eye injuries and/or suspected open globe; pilot uveitis): patients presenting to the Duke Eye Center with active uveitis and microhyphema or hyphema; patients who have independently consented to undergo vitreous tap or biopsy for their uveitis care at the Duke Eye Center.
Exclusion Criteria: Preclinical: subject cannot be a direct report to any of the PIs or other key personnel of this study; pilot (ER): hemodynamically unstable, unable to consent; pilot (Uveitis): unable to consent; cornea or lens opacity/scar which would block the imaging modality.
Information: teresa.hawks@duke.edu

Study: A Phase III Study Assessing the Efficacy and Safety of Intravitreal Injections of 440 ug DE-109 for the Treatment of Active, Non-Infectious Uveitis of the Posterior Segment of the Eye (LUMINA)
Clinicaltrials.gov Identifier: NCT03711929
Sponsor: Santen Inc.
Purpose: This is a phase III study to assess the efficacy and safety of DE-109 440 µg every 2 months in subjects with active, non-infectious uveitis of the posterior segment of the eye (NIU-PS).
Design: Randomized, parallel assignment, quadruple-blind, treatment
Number of Patients: 200
Inclusion Criteria: Noninfectious active uveitis of the posterior segment.
Exclusion Criteria: Females who are pregnant, nursing, or planning a pregnancy; confirmed or suspected infectious uveitis.
Information: clinicaltrials@santen.com

UVEITIS

Study: SAVE-2: Intravitreal Sirolimus as Therapeutic Approach to Uveitis
Clinicaltrials.gov Identifier: NCT01280669
Sponsor: Stanford University, Santen Inc.
Purpose: The purpose of this study is to find out about the safety and effectiveness of 2 different doses the study drug, sirolimus, administered intravitreally in patients with uveitis.
Design: Randomized, parallel assignment, no masking
Number of Patients: 30
Inclusion Criteria: >12 years of age, able to give consent, have diagnosis of uveitis, have active uveitis, defined as having at least 1+ Vitreous Haze and/or at least 1+ Vitreous Cell Count (SUN scale), and: are receiving no treatment; or are receiving: prednisone ≥10 mg/day (or equivalent dose of another corticosteroid), or at least 1 systemic immunosuppressant other than corticosteroids, or combination of prednisone ≥10 mg/day (or equivalent dose of another corticosteroid) and other systemic immunosuppressant. Have inactive disease, defined as having 0.5+ vitreous haze or less and 0.5+ or less vitreous cell count (SUN scale), and are receiving: prednisone <10 mg/day (or equivalent dose of another corticosteroid), or at least 1 systemic immunosuppressant other than corticosteroids, or combination of prednisone <10 mg/day (or equivalent dose of another corticosteroid) and other systemic immunosuppressant. Have posterior, intermediate, or panuveitis; for panuveitis, if an anterior component is present, it must be less than the posterior component. Sufficient inflammation to require systemic treatment and, based on the Investigator's decision, warrants intravitreal treatment. Best-corrected ETDRS visual acuity of 20/400 or better (approximately 20 letters) in the study eye. Best-corrected ETDRS visual acuity of 20/400 or better in the fellow eye (approximately 20 letters).
Exclusion Criteria: Patients with bilateral uveitis who are receiving systemic immunosuppressive therapy (eg, methotrexate, cyclosporine, cyclophosphamide, chlorambucil, mycophenolate mofetil, tacrolimus, or azathioprine) other than prednisone or other corticosteroids for the treatment of uveitis and the uveitis in the fellow eye, in the opinion of the Investigator, cannot be controlled with standard local therapies alone; Any significant ocular disease that could compromise the visual outcome in the study eye. Intravitreal injections (including but not limited to anti-vascular endothelial growth factors 60 days prior to the baseline; Posterior subtenon's or intravitreal injection of steroids 90 days prior to baseline; Intraocular surgery within 90 days prior to day 0 in the study eye; Capsulotomy within 30 days prior to day 0 in the study eye; History of vitreoretinal surgery or scleral buckling within 90 days prior to day 0 in the study eye; Any ocular surgery (including cataract extraction or capsulotomy) of the study eye anticipated within the first 180 days following day 0. Additional exclusion criteria at www.clinicaltrials.org.
Information: ndquan@stanford.edu, lgreer7@stanford.edu

DRY AMD

Study: A Study to Evaluate the Safety, Tolerability and Pharmacokinetics of D-4517.2 After Subcutaneous Administration in Subjects With Neovascular (Wet) Age-Related Macular Degeneration (AMD) or Subjects With Diabetic Macular Edema (DME) (Tejas)
Clinicaltrials.gov Identifier: NCT05387837
Sponsor: Ashvattha Therapeutics, Inc.
Purpose: A study to evaluate the safety, tolerability, and pharmacokinetics of D-4517.2 after subcutaneous administration in subjects with neovascular (wet) age-related macular degeneration (AMD) or subjects with diabetic macular edema (DME).
Design: Nonrandomized, parallel assignment, no masking
Number of Patients: 30
Information: bella@attx.com

Study: Pivotal 2 Study of RGX-314 Gene Therapy in Participants With nAMD (ASCENT)
Clinicaltrials.gov Identifier: NCT05407636
Sponsor: Regenxbio Inc.
Purpose: RGX-314 is being developed as a novel one-time gene therapy for the treatment of neovascular (wet) age-related macular degeneration (wet AMD). Wet AMD is characterized by loss of vision due to new, leaky blood vessel formation in the retina. Wet AMD is a significant cause of vision loss in the United States, Europe and Japan, with up to 2 million people living with wet AMD in these geographies alone. Current anti-VEGF therapies have significantly changed the landscape for treatment of wet AMD, becoming the standard of care due to their ability to prevent progression of vision loss in the majority of patients. These therapies, however, require life-long intraocular injections, typically repeated every four to 12 weeks in frequency, to maintain efficacy. Due to the burden of treatment, patients often experience a decline in vision with reduced frequency of treatment over time. RGX-314 is being developed as a potential one-time treatment for wet AMD.
Design: Randomized, parallel assignment, single masking
Number of Patients: 465
Information: Patientadvocacy@regenxbio.com

Study: A Study of Danicopan in Participants With Geographic Atrophy Secondary to Age-Related Macular Degeneration
Clinicaltrials.gov Identifier: NCT05019521
Sponsor: Alexion Pharmaceuticals
Purpose: This is a dose finding study designed to evaluate the efficacy, safety, and pharmacokinetics of danicopan in participants with GA secondary to AMD. The study consists of a Screening Period of up to 4 weeks, a 104-week masked Treatment Period, followed by an Open-label Extension (OLE) Period starting at Week 104 and lasting for up to 1 year. This study will have 4 treatments arms: 100 milligrams (mg) twice daily (bid), 200 mg bid, 400 mg once daily (qd), and matching placebo.
Design: Randomized, parallel assignment, quadruple masked
Number of Patients: 330
Information: clinicaltrials@alexion.com

Study: A Masked, Placebo-controlled Study to Assess Iptacopan in Age-related Macular Degeneration
Clinicaltrials.gov Identifier: NCT05230537
Sponsor: Novartis Pharmaceuticals
Purpose: The purpose of this study is to assess the effect of Iptacopan to prevent conversion of early or intermediate age-related macular degeneration (AMD) eyes to new incomplete retinal pigment epithelium and outer retinal atrophy (iRORA) or late AMD.
Design: Randomized, parallel assignment, triple masked
Number of Patients: 146
Information: novartis.email@novartis.com

Study: Safety and Tolerability of RPESC-derived RPE Transplantation in Patients With Dry Age-related Macular Degeneration (AMD)
Clinicaltrials.gov Identifier: NCT04627428
Sponsor: Luxa Biotechnology, LLC
Purpose: The main objective of the study is evaluation of the safety and tolerability of RPESC-RPE-4W as therapy for dry AMD.
Design: nonrandomized, sequential assignment, no masking
Number of Patients: 18
Information: jeffreystern@luxabiotech.com

Study: Effect of Oral Curcumin Supplementation in Dry Age-related Macular Degeneration (AMD) Patients
Clinicaltrials.gov Identifier: NCT04590196
Sponsor: University of Illinois at Chicago
Purpose: Oral Longvida curcumin has been shown to accumulate in the retina of human subjects within 10 days of supplementation. This study aims to investigate the duration of oral curcumin supplementation needed to see clinical impact in reducing volume and number of drusen and decreasing choriocapillaris density loss or flow impairment in dry AMD patients.
Design: parallel assignment, quadruple masking
Number of Patients: 40
Information: mehta@uic.edu

Study: FOCUS: First in Human Study to Evaluate the Safety and Efficacy of GT005 Administered in Subjects With Dry AMD
Clinicaltrials.gov Identifier: NCT03846193
Sponsor: Gyroscope Therapeutics
Purpose: This is an open-label first-in-human phase 1/2 multicenter study of GT005 in sub-

jects with macular atrophy due to AMD.
Design: Nonrandomized, sequential assignment
Number of Patients: 35
Information: clinicaltrials@gyroscopetx.com

Study: HORIZON: A Phase 2 Study to Evaluate the Safety and Efficacy of Two Doses of GT005
Clinicaltrials.gov Identifier: NCT04566445
Sponsor: Gyroscope Therapeutics
Purpose: The purpose of this clinical study is to evaluate the safety and efficacy of two doses of GT005 administered as a single subretinal injection in subjects with geographic atrophy secondary to age-related macular degeneration (AMD).
Design: Randomized, parallel assignment
Number of Patients: 180
Information: clinicaltrials@gyroscopetx.com

Study: EXPLORE: A Phase 2 Study to Evaluate the Safety and Efficacy of Two Doses of GT005 (EXPLORE)
Clinicaltrials.gov Identifier: NCT04437368
Sponsor: Gyroscope Therapeutics
Purpose: The purpose of this clinical study is to evaluate the safety and efficacy of two doses of GT005 administered as a single subretinal injection in subjects with geographic atrophy secondary to age-related macular degeneration (AMD).
Design: Randomized, parallel assignment
Number of Patients: 75
Information: clinicaltrials@gyroscopetx.com

Study: Study of Subretinal Implantation of Human Embryonic Stem Cell-Derived RPE Cells in Advanced Dry AMD
Clinicaltrials.gov Identifier: NCT02590692
Sponsor: Regenerative Patch Technologies, LLC
Purpose: The phase 1/2a clinical trial is designed to assess the feasibility of delivery and safety of Human Embryonic Stem Cell-Derived RPE Cells on a parylene membrane (CPCB-RPE1) in patients with advanced, dry age-related macular degeneration.
Design: Single group, no masking
Number of Patients: 16

Study: A Staged Study of the Safety and Effectiveness of ASP7317 in Senior Adults Who Are Losing Their Clear, Sharp Central Vision Due to Dry Age-related Macular Degeneration
Clinicaltrials.gov Identifier: NCT03178149
Sponsor: Astellas Institute for Regenerative Medicine
Purpose: This study is looking at a new treatment for slowing or reversing dry AMD, called ASP7317. ASP7317 is a specially created type of cells derived from stem cells. ASP7317 cells are injected into the macula of the eye. Immunosuppressive medicines (called IMT) are also taken around the time of injection of the cells to prevent the body from rejecting them.
Design: Randomized, parallel assignment, no masking
Number of Patients: 150
Information: astellas.registration@astellas.com

Study: Carbidopa-Levodopa in Dry AMD With Geographic Atrophy
Clinicaltrials.gov Identifier: NCT03451500
Sponsor: Robert W. Snyder, MD, PhD, PC
Purpose: The Investigators will evaluate the safety and tolerability of carbidopa-levodopa in patients with Neovascular AMD and measure the effects on visual acuity and retinal abnormalities due to "wet" (neovascular) AMD. The Investigators will evaluate the safety and tolerability of carbidopa-levodopa in patients with Dry AMD and Geographic Atrophy, and measure the effects on visual acuity, area of geographic atrophy and other retinal abnormalities due to "dry" AMD.
Design: Parallel assignment, randomized, prospective, placebo-controlled
Number of Patients: 7

Study: Study of Photobiomodulation to Treat Dry Age-Related Macular Degeneration (LIGHTSITE III)
Clinicaltrials.gov Identifier: NCT04065490
Sponsor: LumiThera, Inc.
Purpose: This LIGHTSITE III study is a double-masked, sham-controlled, parallel design, prospective multi-site study for the use of PBM as a treatment for visual impairment in subjects with dry AMD.
Design: Randomized, parallel assignment, quadruple masking
Number of Patients: 96
Information: ctedford@lumithera.com, ccroissant@lumithera.com

Study: Safety and Efficacy Study of OpRegen for Treatment of Advanced Dry-Form Age-Related Macular Degeneration
Clinicaltrials.gov Identifier: NCT02286089
Sponsor: Cell Cure Neurosciences Ltd.
Purpose: The main objective of the study is evaluation of the safety and tolerability of OpRegen - human embryonic stem cell-derived retinal pigment epithelial (RPE) cells. The study will also include initial exploration of the ability of transplanted OpRegen cells to engraft, survive, and moderate disease progression.
Design: No masking, single group
Number of Patients: 24
Information: maria@cellcure.co.il; grazag@biotimeinc.com

Study: Study of Subretinal Implantation of Human Embryonic Stem Cell-Derived RPE Cells in Advanced Dry AMD
Clinicaltrials.gov Identifier: NCT02590692
Sponsor: Regenerative Patch Technologies, LLC
Purpose: The phase 1/2a clinical trial is designed to assess the feasibility of delivery and safety of human embryonic stem cell-derived RPE cells on a parylene membrane (CPCB-RPE1) in patients with advanced, dry age-related macular degeneration.
Design: Single Group Assignment, Open
Number of Patients: 20
Information: GAquino@laretina.com

Study: Evaluation of Oral Minocycline in the Treatment of Geographic Atrophy Associated With AMD
Clinicaltrials.gov Identifier: NCT02564978
Sponsor: National Eye Institute
Purpose: To see if minocycline is safe for people with GA and if it helps preserve their vision.
Design: Single Group Assignment, No Masking, Treatment
Number of Patients: 60
Information: Angela.kibiy@nih.gov

Study: METforMIN: Metformin for the Minimization of Geographic Atrophy Progression in Patients With AMD
Clinicaltrials.gov Identifier: NCT02684578
Sponsor: University of California, San Francisco
Purpose: To determine whether metformin, an FDA-approved drug for the treatment of type II diabetes, is a safe and effective treatment to decrease the progression of geographic atrophy in nondiabetic patients with age-related macular degeneration.
Design: Randomized, Safety/Efficacy, Parallel Assignment, Single-Blind, Treatment
Number of Patients: 186
Information: eyestudy@ucsf.edu

WET AMD

Study: Safety and Efficacy of AM712 in Patients With nAMD
Clinicaltrials.gov Identifier: NCT05345769
Sponsor: AffaMed Therapeutics (US) Inc.
Purpose: The purpose of this Phase 1 study is comprised of multiple ascending-dose component (Part 1) and dose-expansion cohorts component (Part 2) to evaluate the safety, tolerability, pharmacokinetics, and efficacy of AM712 in patients with neovascular age- related macular degeneration (nAMD).
Design: Single group, open label
Number of Patients: 24
Information: fan.yang@affamed.com

Study: Phase III Study Assessing the Efficacy, Safety and Immunogenicity of SOK583A1 Versus Eylea in Patients With Neovascular Age-related Macular Degeneration (Mylight)
Clinicaltrials.gov Identifier: NCT04864834
Sponsor: Sandoz
Purpose: To demonstrate similar efficacy, safety and immunogenicity of SOK583A1 and Eylea EU as per Eylea approved treatment regimen in patients with nAMD.
Design: Randomized, parallel assignment, double masked
Number of Patients: 460
Information: novartis.email@novartis.com

WET AMD

Study: Study Evaluating the Treatment of OTX-TKI for Subjects With Neovascular Age-related Macular Degeneration
Clinicaltrials.gov Identifier: NCT04989699
Sponsor: Ocular Therapeutix, Inc.
Purpose: Evaluate the safety, tolerability, and efficacy of OTX-TKI for intravitreal use in subjects with neovascular age-related macular degeneration.
Design: Randomized, parallel assignment, triple masked
Number of Patients: 20
Information: clinicalaffairs@ocutx.com

Study: A Study to Evaluate the Efficacy and Safety of Intravitreal KSI-301 Compared With Intravitreal Aflibercept in Participants With Neovascular (Wet) Age-related Macular Degeneration (wAMD) (DAYLIGHT)
Clinicaltrials.gov Identifier: NCT04964089
Sponsor: Kodiak Sciences Inc
Purpose: This phase 3 study will evaluate the efficacy and safety of KSI-301 compared to aflibercept, in participants with neovascular (wet) age-related macular degeneration (wAMD).
Design: Randomized, parallel assignment, triple masked
Number of Patients: 500
Information: ksi301clinical@kodiak.com

Study: Safety, Tolerability, and Efficacy Study of UBX1325 in Patients With Neovascular Age-Related Macular Degeneration (AMD)
Clinicaltrials.gov Identifier: NCT05275205
Sponsor: Unity Biotechnology, Inc.
Purpose: This study is intended to assess safety, tolerability and biological activity of a repeat IVT injection of UBX1325 in patients with wet AMD.
Design: Parallel assignment, double masking
Number of Patients: 46
Information: UBX1325_medicalmonitor@unitybiotechnology.com

Study: 4D-150 in Patients With Neovascular (Wet) Age-Related Macular Degeneration
Clinicaltrials.gov Identifier: NCT05197270
Sponsor: 4D Molecular Therapeutics
Purpose: Phase 1/2 dose-escalation and randomized, controlled, masked expansion trial in adults with wet AMD undergoing active anti-VEGF treatment.
Design: Randomized, sequential assignment
Number of Patients: 65
Information: clinicaltrials@4DMT.com

Study: A 3-month Study to Compare the Safety of ONS-5010 in Vials Versus Prefilled Syringe in Subjects With Visual Impairment Due to Retinal Disorders (NORSE SEVEN)
Clinicaltrials.gov Identifier: NCT05112861
Sponsor: Outlook Therapeutics, Inc.
Purpose: The study will compare the safety of ophthalmic bevacizumab in vials versus pre-filled syringes in subjects diagnosed with a retinal condition that would benefit from treatment with intravitreal injection of bevacizumab, including exudative age-related macular degeneration, diabetic macular edema, or branch retinal vein occlusion.
Design: Randomized, parallel assignment
Number of Patients: 120

Study: Optical Coherence Tomography Angiography (OCTA) - Directed PDT Triple Therapy
Clinicaltrials.gov Identifier: NCT04075136
Sponsor: Wake Forest University Health Sciences
Purpose: Optical Coherent Tomography Angiography (OCTA)-Directed PDT Triple Therapy for Treatment-Naïve Patients with Exudative Age-related Macular Degeneration (ARMD) versus Standard of Care Anti-VEGF Monotherapy
Design: Randomized, parallel assignment
Number of Patients: 150
Information: angmitch@wakehealth.edu

Study: A Study of The Efficacy And Safety Of The Port Delivery System With Ranibizumab In Patients With Neovascular Age-Related Macular Degeneration Previously Treated With Intravitreal Agents Other Than Ranibizumab (Belvedere)
Clinicaltrials.gov Identifier: NCT04853251
Sponsor: Genentech Inc.
Purpose: Study ML43000 is a Phase 3b/4 multicenter, open-label (visual assessor-masked) study designed to assess the efficacy and safety of PDS 100 mg/mL Q24W in patients with nAMD who have been previously treated with anti-VEGF agents other than ranibizumab. Approximately 200 patients will be enrolled at approximately 40 sites.
Design: Single group assignment, no masking
Number of Patients: 200
Information: global-roche-genentech-trials@gene.com

Study: RGX-314 Gene Therapy Pharmacodynamic Study for Neovascular Age-related Macular Degeneration (nAMD)
Clinicaltrials.gov Identifier: NCT04832724
Sponsor: Regenxbio Inc.
Purpose: RGX-314 is a gene therapy vector carrying a coding sequence for a soluble anti-VEGF protein. RGX-314 is being studied for its potential to have a single injection that could allow the eye to make its own supply of anti-VEGF continually. The purpose of this phase 2, open label study is to evaluate whether different doses of RGX-314 from two different formulations (clinical versus eventual commercial formulation) perform the same in humans when delivered by subretinal administration.
Design: Nonrandomized, sequential assignment, no masking
Number of Patients: 60
Information: patientadvocacy@regenxbio.com

Study: OPT-302 With Ranibizumab in Neovascular Age-related Macular Degeneration (nAMD) (ShORe)
Clinicaltrials.gov Identifier: NCT04757610
Sponsor: Opthea Limited
Purpose: A 2-year, phase 3, multicenter, randomized, parallel-group, sham-controlled, double-masked study. Primary efficacy will be determined at week 52.
Design: Randomized, parallel assignment, quadruple masking
Number of Patients: 990
Information: info@opthea.com

Study: OPT-302 With Aflibercept in Neovascular Age-related Macular Degeneration (nAMD) (COAST)
Clinicaltrials.gov Identifier: NCT04757636
Sponsor: Opthea Limited
Purpose: A 2-year phase 3, multicenter, randomized, parallel-group, sham-controlled, double-masked study. Primary efficacy will be determined at week 52.
Design: Randomized, parallel assignment, quadruple masking
Number of Patients: 990
Information: info@opthea.com

Study: First in Human Study to Evaluate the Safety and Tolerability of EYP-1901 in Patients With Wet Age Related Macular Degeneration (wAMD)
Clinicaltrials.gov Identifier: NCT04747197
Sponsor: EyePoint Pharmaceuticals, Inc.
Purpose: This is a Phase 1 open-label study to assess the bioactivity, ocular and systemic safety, tolerability, and pharmacokinetics of a single injections of EYP-1901 at three dose levels: 440 µg, 2060 µg and 3090 µg.
Design: Nonrandomized, sequential assignment, no masking
Number of Patients: 13
Information: dpaggiarino@eyepointpharma.com

Safety and Bioactivity of AXT107 in Subjects With Neovascular Age-Related Macular Degeneration (SHASTA)
Clinicaltrials.gov Identifier: NCT04746963
Sponsor: AsclepiX Therapeutics, Inc.
Purpose: This is an open-label, dose-escalating, 48-week study assessing the safety, tolerability, bioactivity and duration of action of a single intravitreal injection of 0.1 mg, 0.25 mg, or 0.5 mg AXT107 in approximately 18 subjects (up to 6 subjects per dose) with nAMD.
Design: Nonrandomized, sequential assignment, no masking
Number of Patients: 18
Information: info@asclepix.com

Study: A Study to Evaluate the Long-Term Safety and Tolerability of Faricimab in Participants With Neovascular Age-Related Macular Degeneration (AVONELLE-X)
Clinicaltrials.gov Identifier: NCT04777201
Sponsor: Hoffmann-La Roche
Purpose: This is a multicenter long-term extension study designed to evaluate the long-term safety and tolerability of faricimab

6 milligrams (mg) administered by intravitreal injection at a personalized treatment interval to participants with neovascular age-related macular degeneration who enrolled in and completed one of the Phase III studies: GR40306 (NCT03823287) or GR40844 (NCT03823300), also referred to as the parent studies. Eligible patients who consent to participate in this study will be enrolled upon completion of the end-of-study visit in the parent study.
Design: Single group, no masking
Number of Patients: 1,280
Information: global-roche-genentech-trials@gene.com

Study: Safety and Tolerability Study of Suprachoroidal Injection of CLS-AX Following Anti-VEGF Therapy in Neovascular AMD (OASIS)
Clinicaltrials.gov Identifier: NCT04626128
Sponsor: Clearside Biomedical, Inc.
Purpose: To evaluate the safety and tolerability of suprachoroidally administered CLS-AX following intravitreal anti-VEGF therapy in subjects with neovascular age-related macular degeneration (AMD).
Design: Nonrandomized, sequential assignment, no masking
Number of Patients: 15

Study: Pivotal 1 Study of RGX-314 Gene Therapy in Participants With nAMD (ATMOSPHERE)
Clinicaltrials.gov Identifier: NCT04704921
Sponsor: Regenxbio Inc.
Purpose: This randomized, partially masked, controlled, Phase 2b/3 clinical study will evaluate the efficacy and safety of RGX-314 gene therapy in participants with nAMD. The study will evaluate 2 dose levels of RGX-314 relative to an active comparator. The primary endpoint of this study is mean change in best-corrected visual acuity (BCVA) of RGX-314 relative to ranibizumab. Approximately 300 participants who meet the inclusion/exclusion criteria, will be enrolled into one of 3 arms.
Design: Randomized, parallel assignment, quadruple masking
Number of Patients: 300
Information: patientadvocacy@regenxbio.com

Study: A Study to Comparing SCD411 and Eylea in Subjects With Wet Age-related Macular Degeneration (AMD)
Clinicaltrials.gov Identifier: NCT04480463
Sponsor: Sam Chun Dang Pharm. Co. Ltd.
Purpose: SCD411 is being developed as a biosimilar to the reference product Eylea (aflibercept), an anti-VEGF drug. The study aims to prove equivalence of SCD411 to Eylea in adults with wet AMD, and will look at safety, tolerance, effectiveness, immune response and the movement of the drug through the body.
Design: randomized, parallel assignment, quadruple masking
Number of Patients: 560

Study: MMP-9 Inhibition for Recalcitrant Wet AMD
Clinicaltrials.gov Identifier: NCT04504123
Sponsor: University of Iowa
Purpose: The investigators plan to evaluate the effect of oral doxycycline versus placebo on the anatomic and functional outcomes in persistent sub-retinal eye fluid in neovascular wet age-related macular degeneration. This subset are incomplete or non-responders to current anti-VEGF intravitreal therapy.
Design: Randomized, parallel assignment
Number of Patients: 50
Information: elliott-sohn@uiowa.edu

Study: A Study to Understand Effectiveness and Safety of ABP 938 Compared to Aflibercept (Eylea) in Patients Suffering With Neovascular Age-related Macular Degeneration [Neovascular (Wet) AMD]
Clinicaltrials.gov Identifier: NCT04270747
Sponsor: Amgen
Purpose: The purpose of this study is to compare the efficacy and safety of ABP 938 versus Aflibercept (Eylea) in the treatment of neovascular age-related macular degeneration. Subjects will be randomized in a masked 1:1 ratio to receive 2 mg (0.05 mL) of either ABP 938 (Treatment Group A) or aflibercept (Treatment Group B) administered by intravitreal (IVT) injection.
Design: Randomized, parallel assignment, triple masking
Number of Patients: 566
Information: medinfo@amgen.com

Study: RGX-314 Gene Therapy Administered in the Suprachoroidal Space for Participants With Neovascular Age-Related Macular Degeneration (nAMD) (AAVIATE)
Clinicaltrials.gov Identifier: NCT04514653
Sponsor: Regenxbio Inc.
Purpose: RGX-314 is being developed as a novel one-time gene therapy treatment for the treatment of neovascular (wet) age related macular degeneration (wet AMD).
Design: Randomized, sequential assignment, no masking
Number of Patients: 40
Information: patientadvocacy@regenxbio.com

Study: Study to Gather Information on Safety and Use of High Dose Aflibercept Injection Into the Eye in Patients With an Age Related Eye Disorder That Causes Blurred Vision or a Blind Spot Due to Abnormal Blood Vessels That Leak Fluid Into the Light Sensitive Lining Inside the Eye (PULSAR)
Clinicaltrials.gov Identifier: NCT04423718
Sponsor: Bayer
Purpose: In this study researchers want to learn more about changes in visual acuity (clarity of vision) with a high dose treatment with Aflibercept (Eylea) in patients suffering from neovascular age-related macular degeneration (nAMD). Neovascular AMD is an eye disease that causes blurred vision or a blind spot due to abnormal blood vessels that leak fluid or blood into the light sensitive lining inside the eye (retina). The fluid buildup causes the central part of the retina (macula) responsible for sharp, straight-ahead vision to swell and thicken (edema), which distorts vision.
Design: Randomized, parallel assignment, quadruple masking
Number of Patients: 960
Information: clinical-trials-contact@bayer.com

Study: Study to Assess the Efficacy and Safety of Brolucizumab 6mg Compared to Aflibercept 2 mg in a Treat-to-control Regimen (TALON)
Clinicaltrials.gov Identifier: NCT04005352
Sponsor: Novartis Pharmaceuticals
Purpose: The study is a 64-week randomized, double-masked, multi-center, active-controlled, two-arm study in patients with nAMD (neovascular age related macular degeneration) who have not previously received anti-VEGF (vascular endothelial growth factor) treatment. Patients who consent will undergo screening assessments to evaluate their eligibility based on the inclusion and exclusion criteria.
Design: Randomized, parallel assignment, triple masking
Number of Patients: 692
Information: novartis.email@novartis.com

Study: ADVM-022 Gene Therapy for Wet AMD (OPTIC)
Clinicaltrials.gov Identifier: NCT03748784
Sponsor: Adverum Biotechnologies, Inc.
Purpose: ADVM-022 (AAV.7m8-aflibercept) is a gene therapy product developed for the treatment of neovascular (wet) age-related macular degeneration (wet AMD). Wet AMD is a serious condition and the leading cause of blindness in the elderly. The available therapies for treating wet AMD require lifelong intravitreal (IVT) injections every 4-12 weeks to maintain efficacy. A one-time administration of ADVM-022 has the potential to treat wet AMD by providing durable expression of therapeutic levels of intraocular anti-VEGF protein (aflibercept) and preserving the vision of patients. ADVM-022 is designed to reduce the current treatment burden and the adverse events (AEs) associated with chronic IVT injections.
Design: Nonrandomized, sequential assignment, open label
Number of Patients: 18
Information: stong@adverum.com

Study: NEAMES: Episcleral Brachytherapy for the Treatment of Wet AMD
Clinicaltrials.gov Identifier: NCT02988895
Sponsor: Salutaris Medical Devices, Inc.
Purpose: This is a prospective, single-arm, open-label, safety, usability and tolerability trial of Strontium 90 (Sr90) beta radiation episcleral brachytherapy in subjects receiving aflibercept therapy pro re nata (PRN) for the treatment of early neovascular age-related macular degeneration (nAMD) lesions. Secondary aims are to observe clinical outcomes of area of leakage, subretinal fluid, lesion size, visual acuity, and anti-vascular endothelial growth factor (anti-VEGF) treatment burden.
Design: Single Group, No Masking, Treatment
Number of Patients: 20
Information: mdrew@salutarismd.com

CLINICAL TRIAL UPDATE

WET AMD

Study: RGX-314 Gene Therapy for Neovascular AMD Trial
Clinicaltrials.gov Identifier: NCT03066258
Sponsor: Regenxbio Inc.
Purpose: To test RGX-314's ability to treat neovascular AMD.
Design: Nonrandomized, sequential assignment, no masking, treatment
Number of Patients: 18
Information: patientadvocacy@regenxbio.com

DIABETIC MACULAR EDEMA

Study: Phase 2 Study to Evaluate the Safety and Efficacy of OPL-0401 in Patients With Non-proliferative Diabetic Retinopathy (Spectra)
Clinicaltrials.gov Identifier: NCT05393284
Sponsor: Valo Health, Inc.
Purpose: OPL-0401-201 is a multicenter study to investigate the efficacy and safety of OPL-0401 in patients with diabetes mellitus (DM) with diabetic retinopathy.
Design: Randomized, parallel assignment, triple masking
Number of Patients: 120
Information:

Study: A Study to Evaluate the Safety, Tolerability and Pharmacokinetics of D-4517.2 After Subcutaneous Administration in Subjects With Neovascular (Wet) Age-Related Macular Degeneration (AMD) or Subjects With Diabetic Macular Edema (DME) (Tejas)
Clinicaltrials.gov Identifier: NCT05387837
Sponsor: Ashvattha Therapeutics, Inc.
Purpose: A study to evaluate the safety, tolerability, and pharmacokinetics of D-4517.2 after subcutaneous administration in subjects with neovascular (wet) age-related macular degeneration (AMD) or subjects with diabetic macular edema (DME).
Design: Nonrandomized, parallel assignment, no masking
Number of Patients: 30
Information: bella@attx.com

Study: AG-73305 Single Ascending Dose Cohort Study in DME
Clinicaltrials.gov Identifier: NCT05301751
Sponsor: Allgenesis Biotherapeutics Inc.
Purpose: This is a multi-centered, open-labeled, single ascending-dose-cohort study to evaluate 4 dosing cohorts of AG-73305 administered by intravitreal injection in patients with diabetic macular edema (DME).
Design: Nonrandomized, sequential assignment, no masking
Number of Patients: 25
Information: tan.nguyen@allgenesis.com

Study: A Study to Investigate RO7200220 in Diabetic Macular Edema
Clinicaltrials.gov Identifier: NCT05151731
Sponsor: Hoffmann-La Roche
Purpose: Study BP43445 is a phase II, multicenter, randomized, double-masked, active comparator-controlled study to investigate the efficacy, safety, tolerability, pharmacokinetics, and pharmacodynamics of RO7200220 administered intravitreally in participants with diabetic macular edema. Only one eye will be chosen as the study eye. The duration of the study will be 52 weeks.
Design: Randomized, parallel assignment, triple masking
Number of Patients: 320
Information: global-roche-genentech-trials@gene.com

Study: A Study to Investigate RO7200220 in Combination With Ranibizumab in Diabetic Macular Edema
Clinicaltrials.gov Identifier: NCT05151744
Sponsor: Hoffmann-La Roche
Purpose: Study BP43464 is a phase II, multicenter, randomized, double-masked active comparator-controlled study designed to assess the efficacy, safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of RO7200220 in combination with, anti-vascular endothelial growth factor (VEGF) inhibitor, ranibizumab compared with ranibizumab alone in participants with diabetic macular edema. Only one eye will be chosen as the study eye. The duration of the study will be 52 weeks.
Design: Randomized, parallel assignment, triple masking
Number of Patients: 160
Information: global-roche-genentech-trials@gene.com

Study: Non-Responsive Diabetic Macular Edema and Spironolactone
Clinicaltrials.gov Identifier: NCT04853355
Sponsor: Wake Forest University Health Sciences
Purpose: Diabetic patients with macular edema and choroidal hyperpermeability (as manifested as a thick choroid on OCT (optical coherence tomography) and ICG hyperfluorescence on ICG) unresponsive to anti-VEGF (vascular endothelial growth factor) and steroid injections will be treated with spironolactone in addition to the continued treatment of anti-VEGF injections, specifically aflibercept (Eylea).
Design: Single group, prospective, nonrandomized, pilot study
Number of Patients: 10
Information: mhnelson@wakehealth.edu

Study: A Study to Investigate Faricimab Treatment Response in Treatment-Naive, Underrepresented Patients With Diabetic Macular Edema
Clinicaltrials.gov Identifier: NCT05224102
Sponsor: Genentech, Inc.
Purpose: This phase 4 study is designed to investigate treatment response in treatment-naïve underrepresented patients with diabetic macular edema (DME) who are treated with faricimab. The study population will consist of participants ≥18 years of age who self-identify as Black/African American, Hispanic/Latino American, or Native American/Alaska Native/Native Hawaiian or other Pacific Islander.
Design: Single group, no masking
Number of Patients: 120
Information: global-roche-genentech-trials@gene.com

Study: Multicenter Study on the Efficacy and Safety of OCS-01 in Subjects With Diabetic Macular Edema
Clinicaltrials.gov Identifier: NCT05066997
Sponsor: Oculis
Purpose: The purpose of this study is to evaluate the efficacy and safety of OCS-01 ophthalmic suspension versus vehicle alone in subjects with DME.
Design: Randomized, parallel assignment, double masking
Number of Patients: 482
Information: naleni.eigensatz@oculis.com

Study: A Study to Evaluate THR-687 Treatment for Diabetic Macular Oedema (INTEGRAL)
Clinicaltrials.gov Identifier: NCT05063734
Sponsor: Oxurion
Purpose: This study is conducted to select the THR-687 dose level (Part A of the study) and to assess the efficacy and safety of the selected dose level compared to aflibercept (Part B of the study).
Design: Randomized, parallel assignment, quadruple masking
Number of Patients: 303
Information: info@oxurion.com

Study 212669: A Phase I Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of GSK2798745 in Participants With Diabetic Macular Edema
Clinicaltrials.gov Identifier: NCT04292912
Sponsor: GlaxoSmithKline
Purpose: This is a multi-center, open-label, single arm, 28-day treatment in participants with DME. The study will be composed of 3 periods for all participants: Screening, 28-day Treatment period, and Follow-up visit (approximately 28 days after the final dose).
Design: Single group, no masking
Number of Patients: 54
Information: GSKClinicalSupportHD@gsk.com

Study: Safety, Tolerability and Evidence of Activity Study of UBX1325 in Patients With Diabetic Macular Edema (DME)
Clinicaltrials.gov Identifier: NCT04857996
Sponsor: Unity Biotechnology, Inc.
Purpose: This study is intended to assess the safety, tolerability and evidence of pharmacodynamic activity of a single intravitreal (IVT) injection of UBX1325 in patients with diabetic macular edema (DME).
Design: Randomized, parallel assignment,

double masking
Number of Patients: 62
Information: UBX1325_medicalmonitor@unitybiotechnology.com

Study: Study of the Safety and Efficacy of APX3330 in Diabetic Retinopathy (ZETA-1)
Clinicaltrials.gov Identifier: NCT04692688
Sponsor: Ocuphire Pharma, Inc.
Purpose: The objective of this study is to evaluate the safety and efficacy of APX3330 to treat diabetic retinopathy (DR) and diabetic macular edema (DME).
Design: Randomized, parallel assignment, quadruple masking
Number of Patients: 100
Information: dcoleman@ocuphire.com

Study: First-In-Human Study of CU06-1004 Following Single and Multiple Ascending Doses in Healthy Volunteers
Clinicaltrials.gov Identifier: NCT04795037
Sponsor: Curacle Co., Ltd.
Purpose: This clinical trial is the first-in-human study of CU06-1004. The purpose of this phase 1 study is to assess the safety and tolerability of single and multiple ascending oral doses of CU06-1004 in healthy adult subjects.
Design: Randomized, sequential assignment
Number of Patients: 72
Information: hughlee@kcrnresearch.com

Study: A Study to Evaluate the Safety, Tolerability and Pharmacokinetics of IVT MHU650 in Macular Edema Patients
Clinicaltrials.gov Identifier: NCT04635800
Sponsor: Novartis Pharmaceuticals
Purpose: This open-label study is being conducted to evaluate the initial safety and tolerability of IVT MHU650 in patients with DME, AMD, or RVO. The primary objective of this study is to evaluate the safety and tolerability of single ascending doses of IVT MHU650 in patients with macular edema. The secondary objective of this study is to evaluate the serum pharmacokinetic profile of total MHU650 following single IVT dose of MHU650 in macular edema patients.
Design: Nonrandomized, sequential assignment, no masking
Number of Patients: 18
Information: novartis.email@novartis.com

Study: Safety and Bioactivity of AXT107 in Subjects With Diabetic Macular Edema (CONGO)
Clinicaltrials.gov Identifier: NCT04697758
Sponsor: Asclepix Therapeutics, Inc.
Purpose: This study is an open-label, dose-escalating, 48-week study assessing the safety, tolerability, bioactivity and duration of action of a single intravitreal injection of 0.1 mg, 0.25 mg, or 0.5 mg AXT107 in approximately 18 subjects (up to 6 subjects per dose) with Diabetic Macular Edema (DME).
Design: Nonrandomized, sequential assignment, no masking
Number of Patients: 18
Information: info@asclepix.com

Study: A Study to Evaluate the Long-Term Safety and Tolerability of Faricimab in Participants With Diabetic Macular Edema (Rhone-X)
Clinicaltrials.gov Identifier: NCT04432831
Sponsor: Hoffmann-La Roche
Purpose: This is a multicenter long-term extension study designed to evaluate the long-term safety and tolerability of faricimab administered by intravitreal (IVT) injection at a personalized treatment interval (PTI) to participants who enrolled in and completed one of the two Phase III studies, GR40349 (NCT03622580) or GR40398 (NCT03622593), also referred to as the parent studies.
Design: Single group, no masking
Number of Patients: 1,800

Study: A Study to Investigate Aqueous Humor and Multimodal Imaging Biomarkers in Treatment-Naïve Participants With Diabetic Macular Edema Treated With Faricimab (ALTIMETER)
Clinicaltrials.gov Identifier: NCT04597918
Sponsor: Hoffmann-La Roche
Purpose: This is an exploratory, prospective, multicenter, open-label, single-arm, interventional, Phase IIb study designed to explore the associations over time between clinical assessments, multimodal imaging assessments, aqueous humor (AH) biomarker patterns, and genetic polymorphisms in participants with diabetic macular edema (DME) who are treated with faricimab.
Design: Single group, no masking
Number of Patients: 80
Information: global-roche-genentech-trials@gene.com

Study: A Study of Intravitreal ILUVIEN Implant as Baseline Therapy in Patients With Early Diabetic Macular Edema (DME) (NEW DAY)
Clinicaltrials.gov Identifier: NCT04469595
Sponsor: Alimera Sciences
Purpose: This is a randomized, masked, active-controlled, parallel-group, multi-center study that will assess the efficacy of ILUVIEN as a baseline therapy in the treatment of Center Involving DME (CI-DME). The study will enroll patients who are either treatment naïve or have not received any DME treatments for the preceding 12 months as documented in medical records. Patients who received DME treatment >12 months before screening, must not have received >4 intravitreal injections. The study will compare 2 treatment regimens: ILUVIEN intravitreal implant (0.19 mg) followed by supplemental aflibercept as needed per protocol criteria (2 mg/0.05 mL), compared to intravitreal aflibercept loading dose (2 mg administered by intravitreal injection every 4 weeks for 5 consecutive doses) followed by supplemental aflibercept as needed per protocol criteria (2 mg/0.05 mL).
Design: randomized, parallel assignment, double masking
Number of Patients: 300
Information: rachel.nelson@alimerasciences.com

Study: A Trial to Evaluate the Efficacy, Durability, and Safety of KSI-301 Compared to Aflibercept in Participants With Diabetic Macular Edema (DME) (GLEAM)
Clinicaltrials.gov Identifier: NCT04611152
Sponsor: Kodiak Sciences Inc
Purpose: This phase 3 study will evaluate the efficacy, durability, and safety of KSI-301 compared to aflibercept in participants with treatment-naïve DME.
Design: randomized, parallel assignment, triple masking
Number of Patients: 450
Information: ksi301clinical@kodiak.com

Study: A Study to Evaluate the Efficacy, Durability, and Safety of KSI-301 Compared to Aflibercept in Participants With Diabetic Macular Edema (DME) (GLIMMER)
Clinicaltrials.gov Identifier: NCT04603937
Sponsor: Kodiak Sciences Inc
Purpose: This phase 3 study will evaluate the efficacy, durability, and safety of KSI-301 compared to aflibercept in participants with treatment-naïve DME.
Design: randomized, parallel assignment, triple masking
Number of Patients: 450
Information: ksi301clinical@kodiak.com

Study: RGX-314 Gene Therapy Administered in the Suprachoroidal Space for Participants With Diabetic Retinopathy (DR) Without Center Involved-Diabetic Macular Edema (CI-DME) (ALTITUDE)
Clinicaltrials.gov Identifier: NCT04567550
Sponsor: Regenxbio Inc.
Purpose: RGX-314 is being developed as a novel one-time gene therapy treatment for the treatment of diabetic retinopathy, a chronic and progressive complication of diabetes mellitus. Diabetic retinopathy is a sight-threatening disease characterized in the early stages by neuronal and vascular dysfunction in the retina, and later by neovascularization that leads to further deterioration of functional vision. Despite the availability of current treatments, diabetic retinopathy remains the leading cause of vision loss in working-age adults, those between the ages of 20 and 74. Existing treatment with anti-VEGF agents, although shown to be effective, are limited by short therapeutic half-lives, which then require frequent intravitreal injections over the patient's lifetime, resulting in increased risk of associated adverse events and significant treatment burden. Due to the burden of treatment, patients often do not closely adhere to treatment regimens and experience sub-optimal outcomes and a decline in vision. RGX-314 is being developed as a potential one time treatment for diabetic retinopathy, which may deliver advantages over conventional treatments, such as potentially providing a longer duration of therapeutic effect and intervening at an earlier stage of the disease.
Design: Randomized, parallel assignment, no masking
Number of Patients: 40
Information: patientadvocacy@regenxbio.com

DIABETIC MACULAR EDEMA

Study: A Study to Evaluate THR-149 Treatment for Diabetic Macular Oedema (KALAHARI)
Clinicaltrials.gov Identifier: NCT04527107
Sponsor: Oxurion
Purpose: This study is conducted to select the THR-149 dose level and to assess the efficacy and safety of the selected dose level compared to aflibercept.
Design: Randomized, parallel assignment, quadruple masking
Number of Patients: 122
Information: info@oxurion.com

Study: Study of a High-Dose Aflibercept in Participants With Diabetic Eye Disease (PHOTON)
Clinicaltrials.gov Identifier: NCT04429503
Sponsor: Regeneron Pharmaceuticals
Purpose: The primary objective of the study is to determine if treatment with high-dose aflibercept (HD) at intervals of 12 or 16 weeks provides non-inferior best corrected visual acuity (BCVA) compared to aflibercept dosed every 8 weeks.
Design: Randomized, parallel assignment, quadruple masking
Number of Patients: 640
Information: clinicaltrials@regeneron.com

Study: A Multicenter, Randomized Study in Participants With Diabetic Retinopathy Without Center-involved Diabetic Macular Edema To Evaluate the Efficacy, Safety, and Pharmacokinetics of Ranibizumab Delivered Via the Port Delivery System Relative to the Comparator Arm (PAVILION)
Clinicaltrials.gov Identifier: NCT04503551
Sponsor: Hoffmann-La Roche
Purpose: Study GR41675 is a multicenter, randomized study in participants with diabetic retinopathy without center-involved diabetic macular edema to evaluate the efficacy, safety of the port delivery system with ranibizumab (PDS) relative to the comparator arm.
Design: Randomized, parallel assignment, single masking
Number of Patients: 160
Information: global.rochegenentechtrials@roche.com

Study: Comparative Study of Dexamethasone Implant to Intravitreal Aflibercept in Subjects With Diabetic Macular Edema (PRECISION)
Clinicaltrials.gov Identifier: NCT04411693
Sponsor: The Cleveland Clinic
Purpose: This study is an interventional, prospective randomized study comparing the dexamethasone implant to intravitreal aflibercept. Subjects will have an initial single injection of aflibercept and will be randomized if diabetic macular edema persists. Each subject will be evaluated for 6 months following randomization. Thus, the study duration will be 12 months plus the recruitment period.
Design: Randomized, parallel assignment, no masking
Number of Patients: 50
Information: ehlersj@ccf.org

Study: ADVM-022 Intravitreal Gene Therapy for DME (INFINITY)
Clinicaltrials.gov Identifier: NCT04418427
Sponsor: Adverum Biotechnologies, Inc.
Purpose: A phase 2, multicenter, randomized, double-masked, active controlled study of ADVM-022 (AAV.7m8-aflibercept) in subjects with diabetic macular edema.
Design: Randomized, parallel assignment, quadruple masking
Number of Patients: 33
Information: hjividen@adverum.com

Study: This Study Will Evaluate the Efficacy, Safety, and Pharmacokinetics of the Port Delivery System with Ranibizumab (PDS) in Participants with Diabetic Macular Edema (DME) Compared with Intravitreal Ranibizumab (Pagoda)
Clinicaltrials.gov Identifier: NCT04108156
Sponsor: Hoffmann-La Roche
Purpose: This study will evaluate the efficacy, safety, and pharmacokinetics of the PDS in participants with diabetic macular edema (DME) when treated every 24 weeks (Q24W) compared with intravitreal ranibizumab 0.5 mg every 4 weeks (Q4W).
Design: Randomized, parallel assignment, single masking
Number of Patients: 545
Information: global-roche-genentech-trials@gene.com

Study: The Study to YD312 Tablet in Patients With Diabetic Macular Edema
Clinicaltrials.gov Identifier: NCT03635814
Sponsor: YD Global Life Science Co., Ltd.
Purpose: This study objectives is to evaluate the efficacy of YD312 to improve visual acuity in patients with diabetic macular edema (DME) compared to placebo and determine optimal dose of phase 2b study.
Design: Randomized, parallel assignment
Number of Patients: 100

Study: Multiple Dose Safety and Efficacy of LKA651 in Patients with Diabetic Macular Edema
Clinicaltrials.gov Identifier: NCT03927690
Sponsor: Novartis Pharmaceuticals
Purpose: To evaluate the safety and efficacy of LKA651 in patients with macular edema from diabetic macular edema (DME).
Design: Randomized, parallel assignment, quadruple masking
Number of Patients: 90
Information: Novartis.email@novartis.com

Study: Long Term Safety of Cooling Anesthesia for Intravitreal Injection (COOL-2)
Clinicaltrials.gov Identifier: NCT03956797
Sponsor: Recens Medical, Inc.
Purpose: The purpose of this clinical study is to evaluate the long term safety and efficacy of cooling anesthesia application to the eye as anesthesia for intravitreal injection using a novel cooling anesthesia device.
Design: Randomized, sequential assignment, no masking
Number of Patients: 60
Information: arshad.khanani@gmail.com

Study: Micropulse for Suppression of Diabetic Macular Edema (PULSE)
Clinicaltrials.gov Identifier: NCT03519581
Sponsor: University of California, Davis; IRIDEX Corporation
Purpose: The purpose of this study is to determine if early intervention with micropulse laser treatment in eyes with good visual acuity (20/32 or better) will improve or stabilize vision loss due to the complications of diabetic macular edema.
Design: Randomized, parallel assignment, double masking
Number of Patients: 30
Information: clwallace@ucdavis.edu

Study: Steroid vs Anti-vascular Endothelial Growth Factor for Diabetic Macular Edema Prior to Phacoemulsification (STAMP)
Clinicaltrials.gov Identifier: NCT03832179
Sponsor: Bay Area Retina Associates
Purpose: The primary objective of this study is to compare the efficacy of antecedent intravitreal anti-vascular endothelial growth factor therapy vs Ozurdex in reducing post-cataract surgery related macular edema in patients with pre-existing diabetic macular edema.
Design: Randomized, parallel assignment, no masking
Number of Patients: 32
Information: cluo@bayarearetina.com, fahmed@bayarearetina.com

Study: Anti-VEGF Treatment for Prevention of PDR/DME
Clinicaltrials.gov Identifier: NCT02634333
Sponsor: Jaeb Center for Health Research
Purpose: To determine the efficacy and safety of intravitreous aflibercept injections vs sham injections (observation) for prevention of PDR or CI-DME in eyes at high risk for development of these complications.
Design: Randomized, Safety/Efficacy, Parallel Assignment, Double-Blind, Prevention
Number of Patients: 322
Information: www.jaeb.org

BRIEF SUMMARY OF PRESCRIBING INFORMATION
This Brief Summary does not include all the information needed to use XIPERE™ safely and effectively. See full Prescribing Information for XIPERE™.

XIPERE™ (triamcinolone acetonide injectable suspension), for suprachoroidal use

Initial U.S. Approval: 1957

INDICATIONS AND USAGE

XIPERE™ (triamcinolone acetonide injectable suspension) 40 mg/mL is indicated for the treatment of macular edema associated with uveitis.

CONTRAINDICATIONS

4.1 Ocular or Periocular Infections XIPERE™ is contraindicated in patients with active or suspected ocular or periocular infections including most viral diseases of the cornea and conjunctiva, including active epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, varicella, mycobacterial infections, and fungal diseases.

4.2 Hypersensitivity XIPERE™ is contraindicated in patients with known hypersensitivity to triamcinolone acetonide or any other components of this product.

WARNINGS AND PRECAUTIONS

5.1 Potential Corticosteroid-Related Effects Use of corticosteroids may produce cataracts, increased intraocular pressure, and glaucoma. Use of corticosteroids may enhance the establishment of secondary ocular infections due to bacteria, fungi, or viruses. Corticosteroids should be used cautiously in patients with a history of ocular herpes simplex. Corticosteroids should not be used in patients with active ocular herpes simplex.

5.2 Alterations in Endocrine Function Hypothalamic-pituitary-adrenal (HPA) axis suppression, Cushing's syndrome, and hyperglycemia can occur following administration of a corticosteroid. Monitor patients for these conditions with chronic use. Corticosteroids can produce reversible HPA axis suppression with the potential for glucocorticosteroid insufficiency after withdrawal of treatment. Drug induced secondary adrenocortical insufficiency may be minimized by gradual reduction of dosage. This type of relative insufficiency may persist for months after discontinuation of therapy; therefore, in any situation of stress occurring during that period, hormone therapy should be reinstituted. Metabolic clearance of corticosteroids is decreased in hypothyroid patients and increased in hyperthyroid patients. Changes in thyroid status of the patient may necessitate adjustment in dosage.

ADVERSE REACTIONS

6.1 Clinical Trials Experience Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. XIPERE™ was studied in a multicenter, randomized, sham-controlled, double-masked study in patients with macular edema associated with uveitis. Table 1 summarizes data available from the clinical trial for XIPERE™ treated patients and control patients. The most common ocular (study eye) adverse reactions occurring in ≥ 2% of patients and nonocular adverse reactions occurring in ≥ 5% of patients are shown in Table 1.

Adverse Reaction	XIPERE™ (N = 96) n (%)	Control (N = 64) n (%)
Ocular		
Increased intraocular pressure, non-acute [a,b]	13 (14%)	9 (14%)
Eye pain, non-acute [b]	11 (12%)	0
Cataract [c]	7 (7%)	4 (6%)
Increased intraocular pressure, acute [a, d]	6 (6%)	0
Vitreous detachment	5 (5%)	1 (2%)
Injection site pain	4 (4%)	2 (3%)
Conjunctival haemorrhage	4 (4%)	2 (3%)
Visual acuity reduced	4 (4%)	1 (2%)
Dry eye	3 (3%)	1 (2%)
Eye pain, acute [d]	3 (3%)	0
Photophobia	3 (3%)	0
Vitreous floaters	3 (3%)	0
Uveitis	2 (2%)	7 (11%)
Conjunctival hyperaemia	2 (2%)	2 (3%)
Punctate keratitis	2 (2%)	1 (2%)
Conjunctival oedema	2 (2%)	0
Meibomianitis	2 (2%)	0
Anterior capsule contraction	2 (2%)	0
Chalazion	2 (2%)	0
Eye irritation	2 (2%)	0
Eye pruritus	2 (2%)	0
Eyelid ptosis	2 (2%)	0
Photopsia	2 (2%)	0
Vision blurred	2 (2%)	0
Non-ocular		
Headache	5 (5%)	2 (3%)

[a] Includes intraocular pressure increased and ocular hypertension [b] Defined as not occurring on the day of the injection procedure, or occurring on the day of the injection procedure and not resolving the same day [c] Includes cataract, cataract cortical, and cataract subcapsular [d] Defined as occurring on the day of the injection procedure and resolving the same day

USE IN SPECIAL POPULATIONS

8.1 Pregnancy Risk Summary There are no adequate and well-controlled studies with XIPERE™ in pregnant women to inform drug-associated risks. In animal reproductive studies from the published literature, topical ocular administration of corticosteroids has been shown to produce teratogenicity at clinically relevant doses. There is negligible systemic XIPERE™ exposure following suprachoroidal injection [see Clinical Pharmacology (12.3)]. Corticosteroids should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. Animal Data Animal reproduction studies using XIPERE™ have not been conducted. In animal reproductive studies from the published literature, topical ocular administration of corticosteroids to pregnant mice and rabbits during organogenesis has been shown to produce cleft palate, embryofetal death, herniated abdominal viscera, hypoplastic kidneys and craniofacial malformations.

8.2 Lactation Risk Summary It is not known whether ocular administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in human milk. Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for XIPERE™ and any potential adverse effects on the breastfed infant from XIPERE™. There are no data on the effects of XIPERE™ on milk production.

8.4 Pediatric Use Safety and effectiveness of XIPERE™ in pediatric patients have not been established.

8.5 Geriatric Use No overall differences in safety or effectiveness have been observed between elderly and younger patients following XIPERE™ administration.

NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

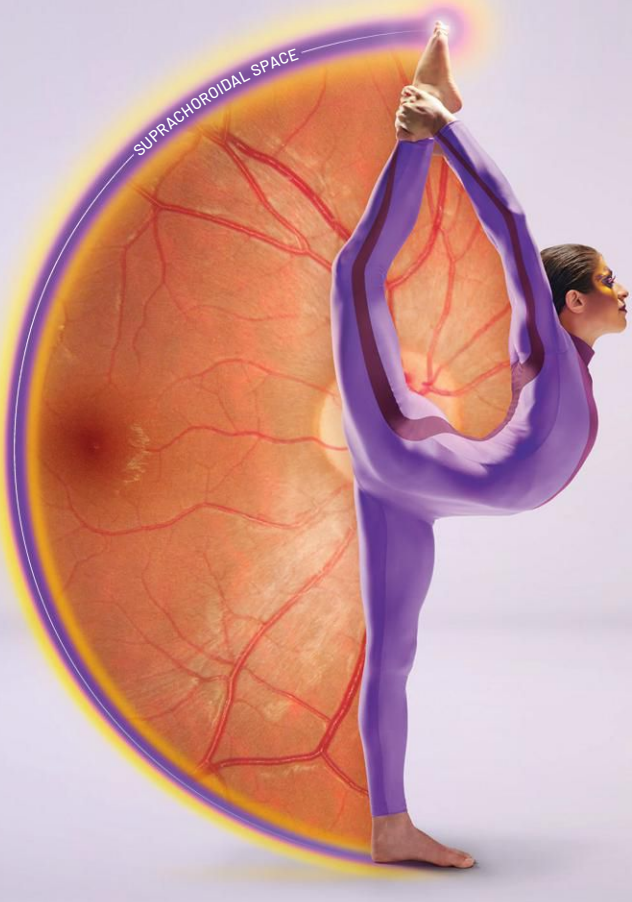
Carcinogenesis No information is available on the carcinogenic potential of triamcinolone acetonide.

Mutagenesis No information is available on the mutagenic potential of triamcinolone acetonide.

Fertility No information is available on the effect of triamcinolone acetonide on fertility.

Manufactured for: Clearside Biomedical, Inc.
900 North Point Parkway, Suite 200
Alpharetta, GA 30005 www.clearsidebio.com/patents

Revised 10/2021 XIP.0015.USA.22 Issued: 02/2022



XIPERE™
(triamcinolone acetonide injectable suspension) 40 mg/mL

POWER MEETS POTENTIAL

When treating uveitic macular edema via the suprachoroidal space,

XIPERE™ can help patients achieve and sustain significant BCVA improvements with a low incidence of IOP elevation[1-3]

See efficacy take center stage at **XIPERE.COM/HCP**

BCVA=best-corrected visual acuity. IOP=intraocular pressure.

Indication

XIPERE™ (triamcinolone acetonide injectable suspension) for suprachoroidal use is a corticosteroid indicated for the treatment of macular edema associated with uveitis.

Important Safety Information

Patients should be monitored following injection for elevated intraocular pressure. See Dosage and Administration instructions in full Prescribing Information.

- XIPERE is contraindicated in patients with **active or suspected ocular or periocular infections** including most viral diseases of the cornea and conjunctiva, including active epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, varicella, mycobacterial infections, and fungal diseases.
- XIPERE is contraindicated in patients with known **hypersensitivity to triamcinolone acetonide** or any other components of this product.
- Use of corticosteroids may produce cataracts, increased intraocular pressure, and glaucoma. Use of corticosteroids may enhance the establishment of secondary ocular infections due to bacteria, fungi, or viruses, and should be used cautiously in patients with a history of ocular herpes simplex.
- Hypothalamic-pituitary-adrenal (HPA) axis suppression, Cushing's syndrome, and hyperglycemia can occur following administration of a corticosteroid. Monitor patients for these conditions with chronic use.
- In controlled studies, the most common ocular adverse reactions were increased ocular pressure, non-acute (14%), eye pain, non-acute (12%), cataract (7%), increased intraocular pressure, acute (6%), vitreous detachment (5%), injection site pain (4%), conjunctival hemorrhage (4%), visual acuity reduced (4%), dry eye (3%), eye pain, acute (3%), photophobia (3%), and vitreous floaters (3%), and in 2% of patients: uveitis, conjunctival hyperaemia, punctate keratitis, conjunctival oedema, meibomianitis, anterior capsule contraction, chalazion, eye irritation, eye pruritus, eyelid ptosis, photopsia, and vision blurred.

  The most common non-ocular adverse event was headache (5%).
- Corticosteroids should be used during pregnancy or nursing only if the potential benefit justifies the potential risk to the fetus or nursing infant.

To report SUSPECTED ADVERSE REACTIONS, contact Bausch + Lomb at 1-800-321-4576 or FDA at 1-800-FDA-1088 or visit www.fda.gov/medwatch.

Please see brief summary of Prescribing Information on adjacent page.

References: 1. XIPERE™ [prescribing information]. Alpharetta, GA: Clearside Biomedical, Inc.; 2021. **2.** Yeh S, Khurana RN, Shah M, et al. Efficacy and safety of suprachoroidal CLS-TA for macular edema secondary to noninfectious uveitis: phase 3 randomized trial. *Ophthalmology*. 2020;127(7):948-955. **3.** Khurana RN, Merrill P, Yeh S, et al. Extension study of the safety and efficacy of CLS-TA for treatment of macular oedema associated with non-infectious uveitis (MAGNOLIA). *Br J Ophthalmol*. 2021;0:1-6.

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