Update on Therapeutic Suprachoroidal Injections

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Disclosures: Clearside, Bausch and Regenxbio (Consultant)
Suprachoroidal delivery
Setting the stage for posterior segment therapies

• 1. Small molecule suspension suprachoroidal delivery shows durability.
  • Triamcinolone, TKI, and complement inhibitor

• 2. Suprachoroidal compartmentalization has potential for safety benefits
  • Triamcinolone - favorable clinical safety data

• 3. Unique ocular distribution creates path forward for other therapies
  • Office-based gene therapy
  • Choroidal disease, e.g. melanoma
Suprachoroidal Delivery

- Triamcinolone [Xipere - Bausch & Lomb]
- Anti-Vegf (tyrosine kinase inhibitor)
- Complement Inhibition
- Gene therapy (NAV AAV-8) [Regenxbio]
- Gene Therapy (DNA nanoparticle)
- Treatment for choroidal tumors [Aura Pharmaceuticals]
Ocular Delivery Methods to Reach the Back of the Eye

Suprachoroidal Injection

SCS Microinjector™ allows for precise delivery into the suprachoroidal space

Suprachoroidal Injection

Intravitreal Injection

Broad diffusion to all areas of the eye including the anterior chamber and lens

Periocular Injection

Highly variable drug diffusion across the sclera into the eye

Subretinal Injection

Invasive surgery with variable results
Core Advantages of Treating Via the Suprachoroidal Space

**TARGETED**

The back of the eye is the location of many irreversible and debilitating visual impairments\(^1\)

**COMPARTMENTALIZED**

Drug is compartmentalized in the suprachoroidal space, which helps keep it away from non-diseased tissues\(^2\)

**BIOAVAILABLE PROLONGED PK**

Fluid spreads circumferentially and posteriorly when injected within the suprachoroidal space, bathing the choroid and adjacent areas with drug\(^2\)

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The Suprachoroidal Space & Triamcinolone Acetonide targeted for efficacy

**Preclinical**

**Clinical Trial**

PEACHTREE Met its Primary Endpoint: Efficacy Data
Subjects gaining ≥15 BCVA letters from baseline, %

Source: Gilger, et al, Treatment of Acute Posterior Uveitis in a Porcine Model by Injection of Triamcinolone Acetonide into the Suprachoroidal Space Using Microneedles, Physiology and Pharmacology
The Suprachoroidal Space & Triamcinolone Acetonide compartmentalized for safety

**Preclinical**

Values are area under the curve ratios (SCS / IVT) over 91 days in rabbit eyes

- **Drug not detected in the aqueous from SCS injection**
- **0.002x**
  - Lens
- **0.03x**
  - Iris and Ciliary Body
- **12x**
  - Sclera/Choroid/Outer Retina
- **1x**
  - Neural Retina

**Clinical Trial**

PEACHTREE IOP AE Rates: Safety Data

- **All 160 Patients**
- **Rescued Control Patients**

The Suprachoroidal Space & Triamcinolone Acetonide prolonged PK for durability

Sources: Gilger, et al, Treatment of Acute Posterior Uveitis in a Porcine Model by Injection of Triamcinolone Acetonide into the Suprachoroidal Space Using Microneedles, Physiology and Pharmacology | Phase 3 PEACHTREE data; MAGNOLIA data
Bausch Health Licenses Clearside Biomedical's XIPERE™ (Triamcinolone Acetonide Suprachoroidal Injectable Suspension), An Investigational Treatment For Macular Edema Associated With Uveitis

October 23, 2019

NDA Resubmission to the FDA Expected to Occur in the First Quarter of 2020

LAVAL, Quebec and ALPHARETTA, Ga., Oct. 23, 2019 /PRNewswire/ -- Bausch Health Companies Inc. (NYSE/TSX: BHC) ("Bausch Health") and Bausch + Lomb, its leading global eye health business, and Clearside Biomedical, Inc. (Nasdaq: CLSD) ("Clearside"), a biopharmaceutical company dedicated to developing and delivering treatments that can restore and preserve vision for people with serious back of the eye diseases, announced today that an affiliate of Bausch Health has acquired an exclusive license for the commercialization and development of XIPERE™ (triamcinolone acetonide suprachoroidal injectable suspension) in the United States and Canada.
AMD Vascular Endothelial Growth Factor Treatment Approaches

Current AMD Therapies Predominantly Focus on VEGF-A Blockade, not VEGF Receptors

- Anti-VEGF-A increases VEGF-C $^1$ & VEGF-D$^2$
- Broad VEGF blockade may improve outcomes
- A Phase 2 study yielded better AMD outcomes with anti-VEGF-A,C,D vs anti-VEGF-A

Suprachoroidal Axitinib May Improve Outcomes with Its Broad VEGF Blockade

- Inhibits VEGFR-1, VEGFR-2, VEGFR-3
- Inhibited corneal, retinal, and choroidal angiogenesis in animal models$^3$$^7$
- More effective than other TKIs for experimental corneal neovascularization in animal models
- Better ocular cell biocompatibility than other TKIs$^8$

Sources:

Suprachoroidal delivery of complement inhibitor small molecule suspension resulted in targeted, compartmentalized, and sustained ocular levels in rabbits.

- **Targeted & Compartmentalized**: High exposure for 90+ days in RPE-choroid-sclera (RCS)
- **Sustained**: Estimated half-life ($T_{1/2}$) of 66, 66, and 76 days at 0.03, 0.1, and 0.3 mg/eye level, respectively
- **Meaningful drug levels**: 3-5 orders of magnitude higher than the in-vitro (AP hemolysis assay) IC90 value (10nM)

**Dutch-Belted pigmented rabbits | n=4-6 eyes/ timepoint | Dose: 0.03, 0.1 and 0.3 mg/eye**
Viral Vectors and the Suprachoroidal Space
Preclinical Activity

Suprachoroidal delivery of NAV AAV8-based gene therapy may avoid injected drug exposure to the vitreous and anterior segment of eye.

SC RGX-314 resulted in similar expression of anti-VEGF Fab

SC RGX-314 resulted in similar activity of anti-VEGF Fab with suppression of VEGF-induced vascular leakage as subretinal delivery.

DNA Nanoparticle Gene Therapy and the Suprachoroidal Space

Potential advantages:
• Efficacy: demonstrated in numerous ocular animal models
  • Transfer large genes (up to ~20 kb)
• Safety: Non-immunogenic, without viral capsid proteins or pre-existing immunity.
  • Potential for repeat dosing
  • Higher doses possible to enhance transfection

Potential synergies with suprachoroidal injection:
• In office, repeat dosing as needed
• Targeted circumferential compartmentalized spread to large surface areas
• Potentially ideal distribution for inherited retinal disease treatment or biofactory approach

Preclinical studies demonstrate SC injections of DNA/polyethylene polylysine nanoparticles (DNPs) may offer the potential for a safe and efficient delivery method
Preclinical SCS and Subretinal Injections of DNA Nanoparticles Produced Comparable Luciferase Activity

Dose: 4mg DNPs/eye  | Suprachoroidal injection (100 uL), Subretinal injection (50 uL)
DNPs consisted of a single copy of plasmid DNA with a polyubiquitin C/luciferase transcriptional cassette

Source: Szilárd Kiss, MD, Macula Society Presentation February 2019
Aura Biosciences Announces Updated Phase 1b/2 Clinical Data for AU-011 Presented at the American Academy of Ophthalmology 2019 Annual Meeting

October 15, 2019

Light-Activated AU-011 has the Potential to be the First FDA Approved Therapy for the Primary Treatment of Choroidal Melanoma

Exploring Suprachoroidal Delivery for AU-011

Amy C. Scheffer, M.D., Weill Cornell Medical College and Retina Consultants of Houston, gave an oral presentation highlighting the data from the ongoing Phase 1b/2 study with intravitreal administration as well as new preclinical research demonstrating the potential advantages of delivering AU-011 using the suprachoroidal route of administration. Aura recently executed a licensing agreement with Clearside Biomedical for use of Clearside’s suprachoroidal space (SCS) Microinjector™ for the treatment of intracocular cancers. Aura believes that by delivering AU-011 into the SCS, there is the potential for treating a larger number of patients with a good safety profile and a greater range of tumor sizes. Preliminary preclinical pharmacology data showed that AU-011 administered via the SCS Microinjector achieved full necrosis of tumor cells in all animals following laser activation. Further preclinical studies are currently ongoing and Aura expects to initiate clinical testing using suprachoroidal delivery for AU-011 during the first half of 2020.

Ocular Oncology and the Suprachoroidal Space
Aura Biosciences: Press Release, 10/15/2019

Treatment: Proprietary viral-like particle bioconjugates (VPB), activated with an ophthalmic laser. VPBs bind selectively to unique receptors on cancer cells in the eye.
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