Suprachoroidal delivery of CLS-301, a potent small molecule integrin antagonist, offers multi-month durability and high bioavailability in the chorioretina

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Purpose and Scientific Rationale

- The purpose of this work was to assess safety, durability and compartmentalization of suprachoroidally administered small molecule suspension of a potent integrin antagonist (CLS-301).
- Integrins play a major role in diverse biologic as well as pathologic processes such as cell adhesion/migration, angiogenesis, and immune responsiveness.[1,2] In diabetic macular edema (DME), integrin-inhibtion may have broader therapeutic advantages over existing anti-VEGF-A monotherapies.[3]
- Drug delivery to the suprachoroidal space (SCS®) is a clinical reality after the 2021 FDA approval of a triamcinolone acetonide injectable suspension for suprachoroidal (SC) use (XIPERE®), administered via a microneedle-based device, the SCS Microinjector®.
- The SCS Microinjector® offers an office-based procedure for SC delivery. Suspension formulation delivered into the SCS has potential for long-acting, targeted, compartmentalized drug delivery with high bioavailability to the chorioretina.

SCS Microinjector®, with 900 µm needle connected

Materials & Methods

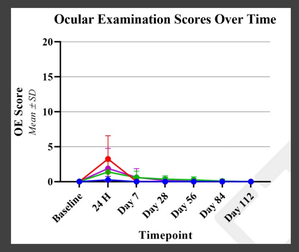
- Formulation: A single carboxymethyl cellulose (CMC)-based aqueous suspension formulation of CLS-301 (20 mg/mL, for PK study 1), and (80 mg/mL, for PK study 2) was prepared and stored refrigerated at 4° C until use. The 80 mg/mL formulation was further diluted appropriately with vehicle to 60 mg/mL and 40 mg/mL concentrations.
- This non-GLP study complied with the study protocol and Powered Research Standard Operating Procedures (SOPs).
- A single bilateral suprachoroidal injection (100 µL) of CLS-301 suspension (2, 4, 6, and 8 mg/eye) was administered into the SCS of Dutch-Belted (DB) pigmented rabbits (n=12/group) using the SCS Microinjector in 2 independent rabbit studies.
- Ocular tolerability was assessed via clinical observations including slit-lamp and indirect ophthalmoscopy throughout the study duration.
- Ocular tissues [RPE-choroid-sclera (RCS), retina, vitreous humor, aqueous humor; n=4/timepoint], and blood were collected on days 1, 7, 28, 56, 84 (only PK study 2) and 112.
- Eyes (n=4) were collected for histology on day 112 for all 3 dose levels in PK study 2. Noninjected eyes (n=4) were used as control for histology assessment.
- An 8-mm biopsy punch was used to collect the central retina and central RCS around the optic nerve head.
- Ocular tissues were homogenized and analyzed for drug levels using a liquid chromatography tandem mass spectroscopy (MS-MS) system.

Results

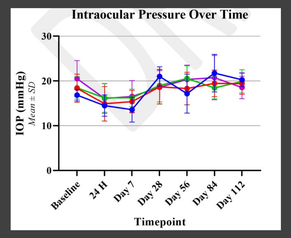
1 Ocular Tolerability

- ✓ No overt signs of toxicity or intraocular inflammation were observed in rabbits during 16-week studies

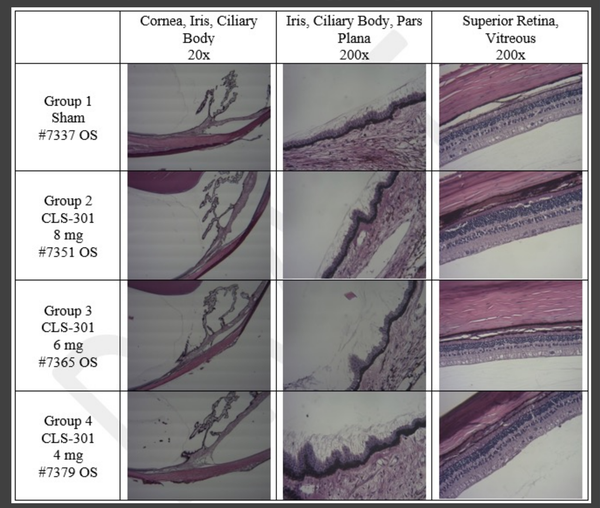
Ocular Exam Scores



Intraocular Pressure



Representative histology images (1 month)

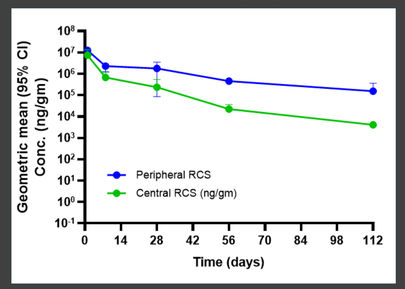


Data from PK study 2 ; similar trends were observed in PK study 1 at lower dose (2 mg)

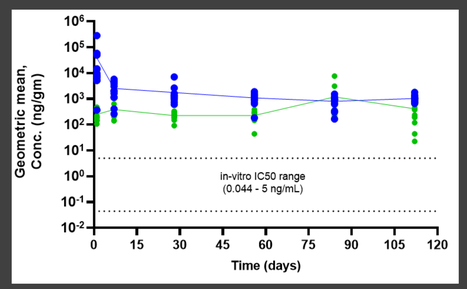
2 Targeted Bioavailability and Durability

- ✓ High and durable bioavailability in the chorio-retina tissues
- ✓ Retina drug levels were maintained above in-vitro IC50 values (0.044-5 ng/mL) for at least 16-weeks (the last study timepoint)
- ✓ Drug levels in central RCS and central retina suggests potential for submacular drug delivery

PK: Drug depot levels in RCS
Dose: 2 mg/eye



PK: Drug levels in Retina
Dose: 4, 6, 8 mg (pooled data)



3 Compartmentalization

- ✓ The highest drug levels were observed in the RCS (dose-depot) followed by retina (target tissues).
- ✓ Sporadic and/or minimal drug levels detected in the vitreous humor and aqueous humor; negligible drug levels in plasma.

Key Findings

- ✓ SC injected CLS-301, a small molecule suspension of a potent integrin antagonist, at studied dose levels and duration, was well-tolerated in rabbits.
- ✓ Drug levels in central RCS and central retina confirmed posterior spread of injectate into the SCS after the SC injection and supports potential for submacular delivery via SC administration.
- ✓ SC injected CLS-301 achieved pharmacologically meaningful and durable drug levels in the retina.
- ✓ Importantly, mean drug levels in the central retina were maintained 30- to 550-folds higher than the in-vitro IC50 values (0.5-5 ng/mL, blocking of cell adhesion to vitronectin) for at least 4 months. On day 112 (C_{last}), the mean drug levels in the central retina (674 ng/gm) and peripheral retina (955 ng/gm) were 1-2 orders of magnitude higher than in-vitro IC50 values.
- ✓ SC injected CLS-301 exhibited high dose-depot level in RCS for the entire duration of the study. Hence, CLS-301 has a potential to be a long-acting delivery system via SC administration.
- ✓ Sporadic low drug levels were detected in vitreous humor, and aqueous humor. This compartmentalized ocular drug distribution after SC administration may avoid any potential off-target ocular side effects.
- ✓ SC injection of CLS-301 resulted in negligible systemic (plasma) drug levels.

Conclusions

- ❖ Suprachoroidal delivery of CLS-301 offers targeted, compartmentalized, and durable drug delivery to the chorioretina. This trend is consistent with other small molecule suspensions injected into the SCS.
- ❖ SC CLS-301 has potential to address some of the efficacy, and treatment burden limitations of current therapies.
- ❖ Further preclinical and clinical studies exploring long-term safety, pharmacology and toxicology of CLS-301 are warranted.

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