PROGRAM #:
4002 - B0180

PHARMACOKINETICS INCLUDING OCULAR DISTRIBUTION CHARACTERISTICS OF SUPRACHOROIDALLY ADMINISTERED CLS011A IN RABBITS COULD BE BENEFICIAL FOR A WET AMD THERAPEUTIC CANDIDATE

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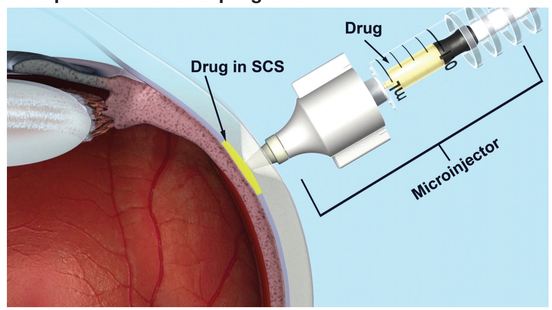
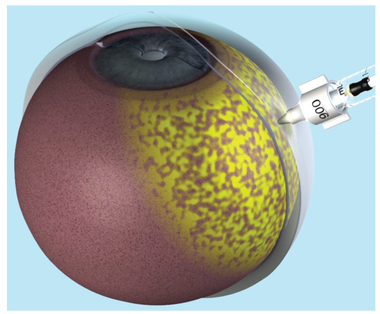
PURPOSE

Neovascular age-related macular degeneration (AMD) is a leading cause of blindness in people over the age of 55 years in the western world.[1] Although the emergence of anti-VEGF therapies has revolutionized the treatment of neovascular AMD, a significant unmet need persists for optimal visual response and durability of the response in all patients.[2] Dual targeting of VEGF and PDGF-β signaling pathways has shown synergistic inhibition of angiogenesis in ocular neovascularization models compared to anti-VEGF monotherapy and inhibition of PDGF binding to its receptor has been demonstrated to interfere with pericyte induced anti-VEGF resistance.[3,4] CLS011A is a small molecule with anti-VEGFr and anti-PDGFr binding properties. The purpose of this study was to assess the pharmacokinetics and ocular tissue distribution following a single bilateral suprachoroidal injection of 4 mg CLS011A to each eye of pigmented Dutch Belted rabbits.

INTRODUCTION

- Clearside Biomedical, Inc., headquartered in Alpharetta, GA, is a clinical-stage biopharmaceutical company developing first-in-class drug therapies to treat blinding diseases of the eye.
- Using proprietary microinjection technology, Clearside Biomedical targets drugs to the retina and choroid by administering drugs through the suprachoroidal space (SCS).
- Suprachoroidal dosing for the treatment of eye diseases has several potential advantages including high bioavailability, and differentiating efficacy and safety.
- Clearside currently has 3 development programs: a non-infectious uveitis program currently enrolling a Phase 3 clinical study; an RVO program that recently completed a Phase 2 clinical study; and a pre-clinical AMD program.



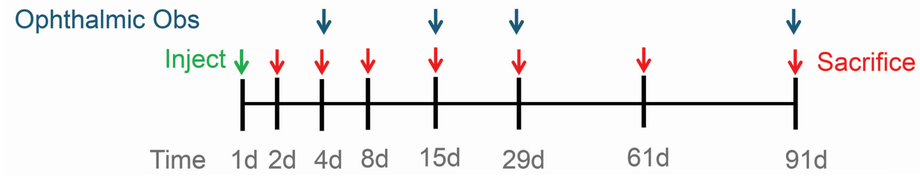


Injected drug formulation spreads around the eye in the suprachoroidal space (SCS).

METHODS

Study Design

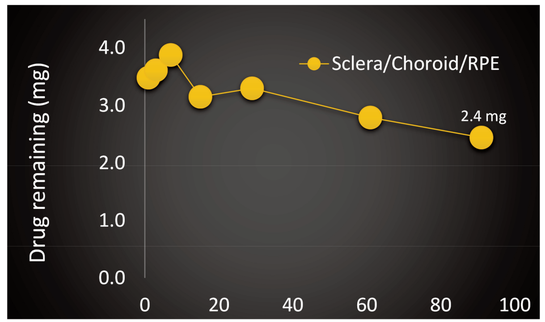
Groups	Route	Dose (mg)	N/timepoint (Animals/Eyes)	Endpoints
1	SCS	4 mg	2/4	Exams Drug level in tissues



On Day 0, 14 male rabbits were administered a single bilateral suprachoroidal injection of CLS011A. Ophthalmic exams occurred pre-dose and on Study Days 4, 15, 28, and 91 prior to sacrifice, as applicable.

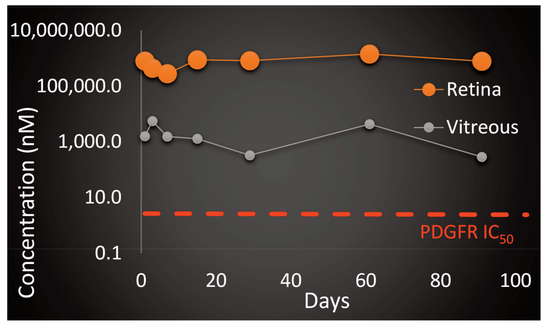
On specified days through Study Day 91, two animals/time point were euthanized for the collection of blood for plasma and ocular tissues: aqueous humor, vitreous humor, retina, and sclera/choroid-RPE. Plasma and ocular tissues were analyzed for concentrations of CLS011A by the Covance Madison Discovery Bioanalytical Department using LC-MS/MS.

RESULTS



At 3 months > 60 % of CLS011A remaining

Half life > 3 months



Retina levels greater than 1 million fold above IC_{50} of VEGFR and PDGFR

Plasma levels below quantification limit: < 1 ng/mL

RESULTS

- Suprachoroidal administration of CLS011A at 4 mg/eye (100 µL/injection) was well tolerated through Study Day 91.
- No overt signs of toxicity were observed. CLS011A was not detected at quantifiable levels in either plasma or aqueous humor samples.
- CLS011A was quantifiable at all time points in the vitreous humor, retina, and sclera/choroid-RPE (SCR).
- A concentration gradient of CLS011A in tissues was present, with the SCR being highest, followed by the retina, and finally the vitreous humor with the lowest concentrations.
- The elimination half-life was calculated to be 102 days and more than 60% of CLS011A remained in the SCR at 3 months post injection.

CONCLUSIONS

- A single bilateral suprachoroidal administration of 4 mg/eye CLS011A was well tolerated in the pigmented Dutch Belted rabbit.
- Systemic exposure to CLS011A was minimal, and absorption of CLS011A into the posterior segment of the eye was observed with minimal CLS011A exposure to the anterior segment of the eye.
- The calculated half-life in the SCR is greater than 3 months and the retina levels are greater than 1 million fold above the IC_{50} of CLS011A for VEGFr and PDGFr.
- These data suggest that suprachoroidal drug injection results in distribution and duration of CLS011A that could be beneficial for an agent with an extended duration for the potential treatment of a retinal disease such as neovascular age-related macular degeneration.

REFERENCES

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4. Giddabasappa A, Lalwani K, Norberg R, et al. Axitinib inhibits retinal and choroidal neovascularization in *in vitro* and *in vivo* models. *Exp Eye Res* 2016;145:373-379.