In Vitro and *In Vivo* Characterizations of GB-401, a Sustained-Release Intravitreal Implant Containing a Novel Beta-Adrenergic Antagonist Prodrug for Primary Open-Angle Glaucoma (POAG)

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BACKGROUND AND PURPOSE

- Intraocular pressure (IOP) elevation and fluctuation is a major risk factor for glaucoma progression and vision loss. Non-adherence or poor topical anti-glaucoma drug penetration in patients with POAG is correlated to disease progression. Topical beta-adrenergic antagonists are effective in reducing IOP but may be associated with systemic adverse events.
- GB-401 is a biodegradable implant containing a novel beta-adrenergic antagonist prodrug that has the potential to enable sustained IOP reduction with twice-yearly intravitreal (IVT) injections.
- The novel beta-adrenergic antagonist prodrug was synthesized by conjugating hydrophobic linkers to the parent beta-adrenergic antagonist (timolol). This prodrug has been shown to effectively reduce IOP in an ocular hypertensive rat model (Hoang et al., ARVO 2019).
- This study includes *in vitro* characterization of GB-401 and *in vivo* evaluation for pharmacokinetics (PK) and ocular toxicity.

METHODS

In Vitro Characterization

- Implant loading and delivery through 23G needle were tested.
- *In vitro* drug release in phosphate buffered saline at 37°C was evaluated.

Pharmacokinetics Study

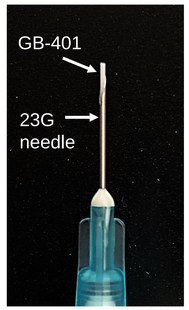
- GB-401 implants were injected via IVT route in Dutch-belted rabbits at two dose levels.
- Ocular tissues and blood samples were collected at various timepoints and analyzed for drug concentrations.

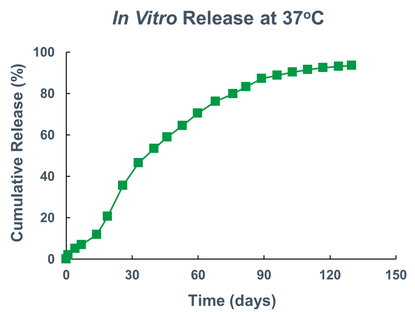
Ocular Toxicity Study

- A repeat-dose GLP toxicity study in minipigs at two dose levels injected via IVT route is ongoing.
- The second dose was administrated ~4 months (127 days) after the first dose.
- Imaging and ophthalmic exams (OE) were performed on Day 3 (OE only), 7, 28, and 84 post-dose.
- Necropsy is scheduled for week 37.

RESULTS

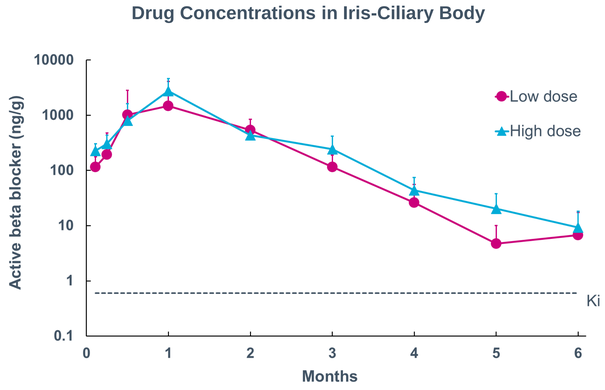
In Vitro Characterization





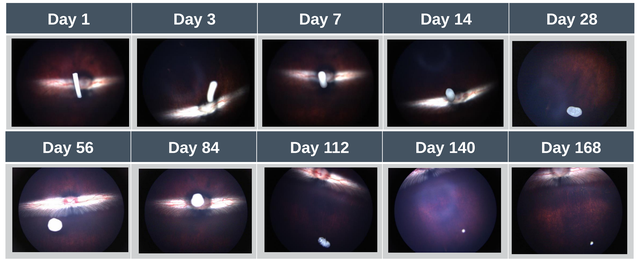
- GB-401 is a small cylindrical rod that is delivered via a 23G needle.
- Sustained drug release from GB-401 lasted at least 120 days *in vitro.*

Pharmacokinetics Study in Dutch-belted Rabbits



- Pharmacologically active drug levels were achieved in target ocular tissues throughout 6 months following IVT injection of both low and high doses.
- No drug was detected in plasma at any time point.
- The PK data demonstrated a durability of 6 months for GB-401 in rabbit vitreous.

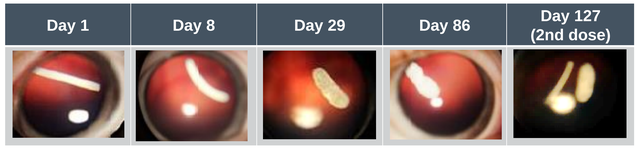
Representative Implant Images in the Vitreous of Dutch-belted Rabbits



- GB-401 gradually degraded over ~6 months in rabbit vitreous.
- This biodegradable implant formulation was well tolerated in rabbit eyes.

Repeat-dose Ocular GLP Toxicity Study in Minipigs

Representative Implant Images in the Vitreous of Minipigs



Note: the implants in the images have been magnified.

- GB-401 appears to degrade slower in minipigs than in rabbits, suggesting a potential longer durability in minipigs.
- On day 127, the 2nd dose was administrated to demonstrate safety of repeat doses while the 1st dose had not fully degraded.
- GLP toxicity study in minipigs is ongoing and no signs of ocular toxicity have been observed to date.

CONCLUSIONS

- GB-401 is a sustained-release biodegradable intravitreal implant containing a novel prodrug of timolol.
- GB-401 has the potential to enable sustained IOP reduction with twice-yearly injections in patients with POAG, without the systemic side effects of beta-adrenergic antagonists.
- A Phase 1/2a first-in-human trial is being planned.

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