A Novel Injectable Intravitreal (IVT) Depot Formulation of a Beta-Adrenergic Prodrug as a Potential Sustained-Delivery Treatment in Primary Open Angle Glaucoma (POAG)

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Background and Purpose

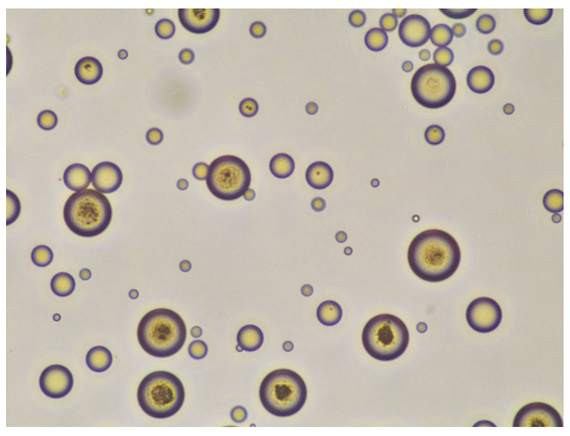
- Reduction in intraocular pressure (IOP) is the only proven treatment to prevent progression of vision loss associated with POAG.
- Topical eye drops for POAG are limited by poor patient compliance and low drug bioavailability/residence time on the corneal surface.
- GB-401 is an injectable formulation of a beta-adrenergic antagonist prodrug (GBV-6249-192) designed to enable sustained IOP reduction for up to 6 months with a single IVT administration.
- This study evaluates the *in vitro* and *in vivo* performance of GB-401, including pharmacokinetics, ocular safety, and IOP-lowering efficacy in preparation of a Phase 1/2a first-in-human clinical study.

Methods

- GBV-6249-192 prodrug was synthesized by conjugation of hydrophobic linkers to the parent compound to enhance drug encapsulation.
- Drug-loaded GB-401 biodegradable microparticles (MP) were produced and surface-modified to facilitate particle aggregation *in vivo* in order to prevent possible interference with the visual axis.
- The particle size, drug loading, and particle aggregation of GB-401 were assessed *in vitro*.
- Pharmacokinetics were evaluated in Dutch-belted rabbits at two dose levels following a single IVT or subconjunctival (SC) injection of the MP formulation. Target ocular tissues and blood samples were collected at various timepoints and drug concentrations were quantified by liquid chromatography/mass spectrometry.
- Experimental ocular hypertension (OHT) was induced by injecting hypertonic saline via the episcleral veins in the left eye of brown Norway rats twice over a period of two weeks. The MP formulation was administrated by a single IVT or SC injection in the left eye at two dose levels. IOP was measured in both eyes prior to the MP injection and on Days 2, 7, 14, 21 and 28 using a Tonopen. Both eyes in all animals were examined and scored using a Draize/McDonald-Shadduck scoring system and ocular histology.

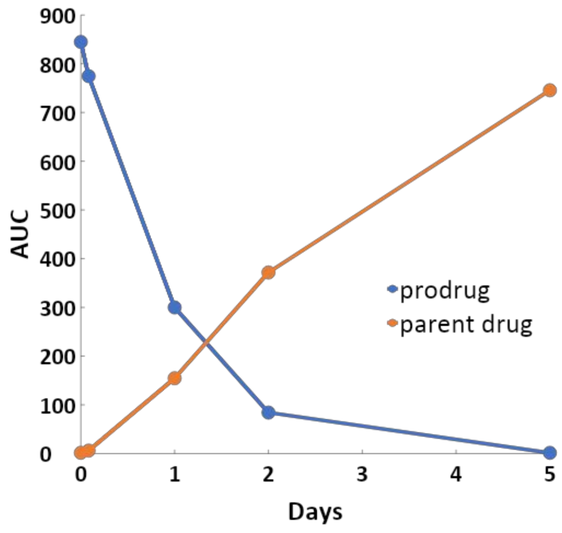
Results

Particle Characterization

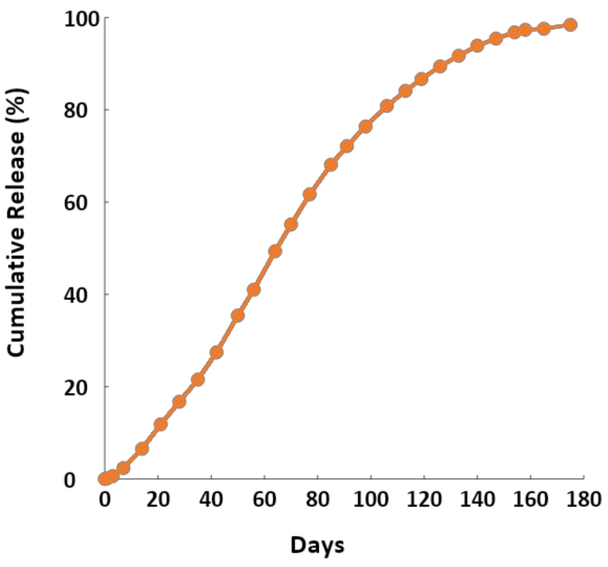


- Mean MP size = 27-30 µm (volume %)
- High drug loading of 28-31% (w/w); > 90% encapsulation efficiency

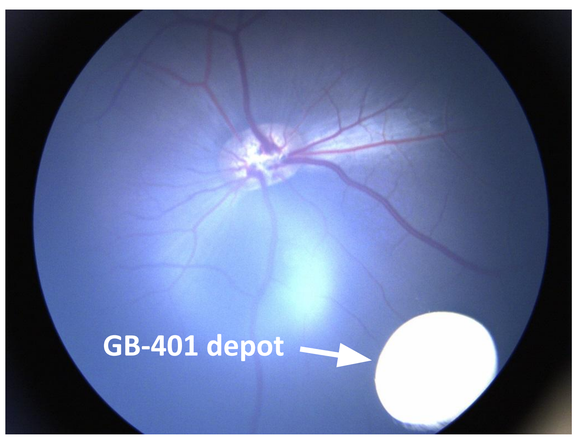
Prodrug Stability



In Vitro Drug Release



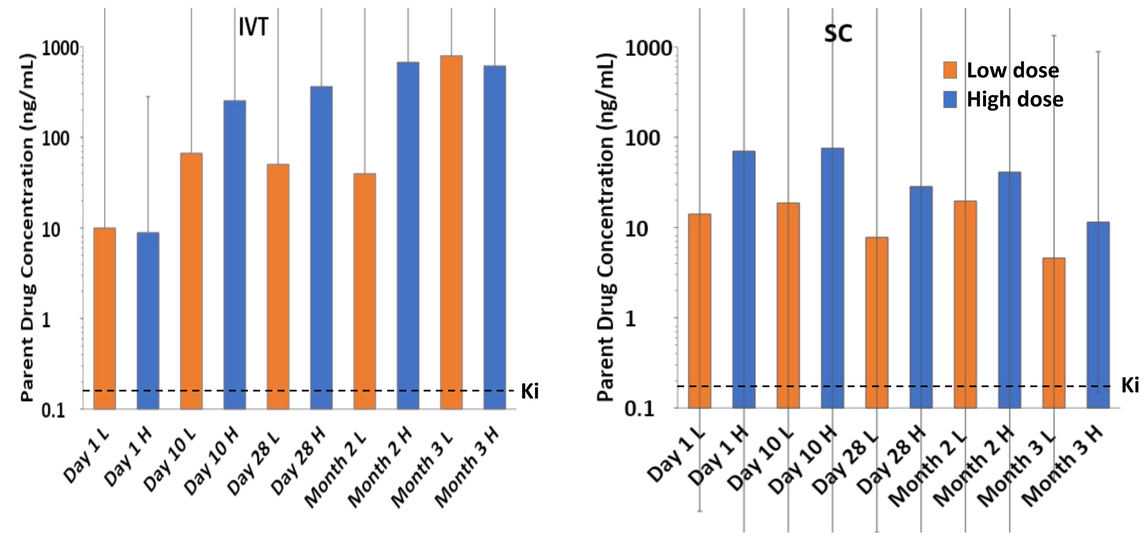
Depot Formation



- Color fundus microscopy of mini-pig vitreous revealed microparticles aggregated into a discrete depot upon IVT injection

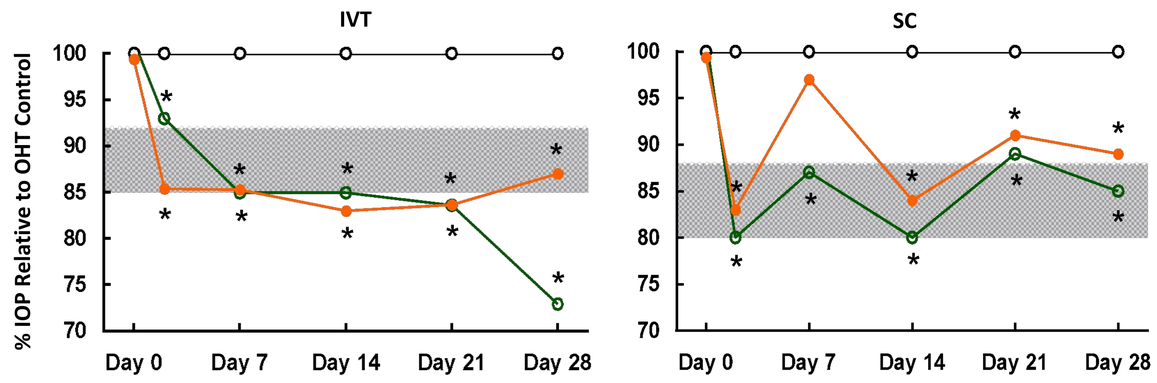
- GB-401 achieved high drug loading, encapsulation efficiency, and tunable sustained drug release kinetics owing to the modified physiochemical properties over the parent compound.
- The pro-drug linker of GBV-6249-192 degrades by hydrolysis, allowing full conversion of the inactive prodrug to the active parent compound.
- *In vitro* drug release lasted over a period of approximately 180 days.
- The MP coalesced into a solid, discrete depot upon injection.

Pharmacokinetics



- Ongoing pharmacokinetic study revealed therapeutic levels of parent drug were achieved in iris-ciliary body (ICB) from day 1 and sustained past 3 months in both IVT and SC groups.
- Higher and more prolonged parent drug concentration in ICB via IVT route.
- Neither parent compound nor prodrug was detected in plasma at any timepoint.

Efficacy in a Rat Ocular Hypertension Model



- Drug-loaded MP provided sustained reduction in IOP via IVT and SC
- IVT Route = 7-28% IOP reduction vs OHT control; SC route = 12-20%
- No signs of ocular toxicity.

Conclusions

- Sustained ocular drug levels and IOP reduction were achieved after a single IVT or SC injection of GB-401 in experimental animal models.
- GB-401 may potentially provide sustained reduction of IOP for up to 6 months with a single injection and may lead to a new long-term treatment in patients with POAG.
- A Phase 1/2a first-in-human study is planned.