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An Injectable Formulation of a Beta-Adrenergic Antagonist Prodrug for Sustained Reduction of Intraocular Pressure (IOP)

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Background and Purpose

- Long-lasting therapeutics that effectively lower and maintain intraocular pressure (IOP) remain a substantial unmet medical need
- A prodrug (GB-6249-192) of a beta-adrenergic antagonist was designed and synthesized by conjugation of a hydrophobic linker
- The prodrug was encapsulated into biodegradable polymeric microparticles (MP) for sustained delivery
- This study elucidates the *in vitro* characteristics of the prodrug and its microparticle formulation and the *in vivo* pharmacokinetics and efficacy in IOP reduction

Methods

Physicochemical Characterization

- *In vitro* degradation of the prodrug and drug release from MP were evaluated in phosphate buffered saline at 37 °C
- Prodrug and parent drug concentrations were analyzed by LC/MS
- Particle size was assessed using a Beckman Coulter Counter

Pharmacokinetics

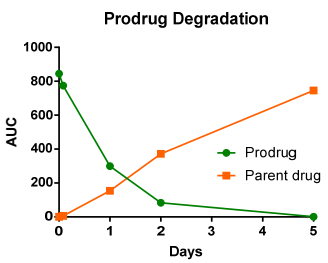
- Drug-loaded MP were injected via either subconjunctival (SC) or intravitreal (IVT) route at two dose levels in Dutch-Belted rabbits
- At various time points, ocular tissues were collected and drug levels were measured by LCMS/MS

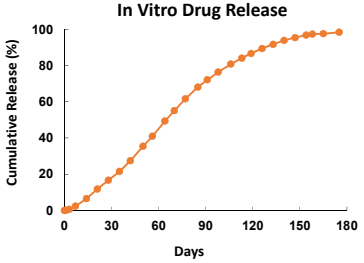
Efficacy

- Experimental ocular hypertension (OHT) was induced in brown Norway rats by injecting hypertonic saline via the episcleral veins in the left eyes twice over two weeks
- Drug-loaded MP formulation was administrated by a single SC or IVT injection in the left eyes at two dose levels
- IOP was measured in both eyes prior to the MP injection and on Days 2, 7, 14, 21 and 28
- All eyes were examined and scored using a combined Draize and McDonald-Shadduck scoring system

Results

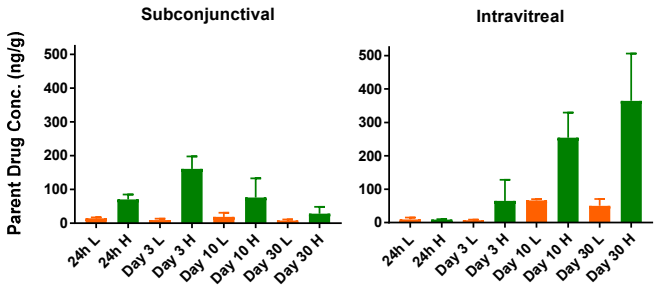
Physicochemical Characterization





- The prodrug linkage was completely hydrolyzed in 4-5 days with release of parent compound
- MP afforded sustained drug release for 6 months *in vitro* at 37°C
- Mean MP size was 27-30 µm in diameter (by volume)
- High drug loading of 28-31% (w/w); > 90% encapsulation efficiency

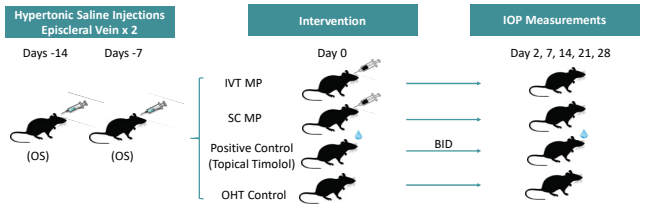
Pharmacokinetics in Dutch-Belted Rabbits



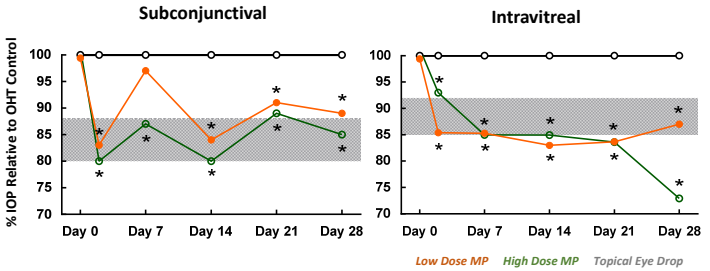
Drug concentrations in iris-ciliary body (ICB) after SC or IVT injection

- Therapeutic levels of parent compound were achieved in target ocular tissues throughout 28 days following IVT or SC injection of low or high dose MP
- Neither prodrug nor parent drug was detected in serum at any time point
- No test article-related toxicity at either dose or either route of administration
- Higher parent drug levels were detected in ICB after IVT injection

Efficacy in a Rat Ocular Hypertension Model



Schematic of the efficacy study design in a rat OHT model



- Drug-loaded MP provided sustained reduction in IOP via IVT and SC
- SC route: IOP reduction = 12-20% vs OHT control
- IVT route: IOP reduction = 7-28% vs OHT control

Conclusions

- The injectable MP formulation of a beta-adrenergic antagonist prodrug provides sustained IOP reduction for 28 days and may lead to a new long-lasting and effective treatment for ocular hypertension.
- SC or IVT injection of the MP formulation was well tolerated in brown Norway rats at the tested doses.