Transitioning a drug-led combination product through the FDA: the Purgo Pouch, FDA Interactions, and Meeting a Major Unmet Need of Biofilm-Complicated, Fracture-Related Infections

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Introduction

Treatment of bone fracture-related infection (FRI) remains a major unmet need. Soldiers in recent and current conflicts have suffered some of the highest rates of these infections, and FRI in civilians persists. Systemic therapies fail for at least two reasons: 1) antibiotics do not reach the trauma site due to compromised vasculature, and 2) antibiotics that do reach the site are at an insufficient level to kill biofilms. Current local antibiotic therapies are used off-label but cannot sustain high dose concentrations. We are developing the Purgo Pouch to address these limitations. The Purgo Pouch is a refillable drug delivery device that sustains local, high-dose antibiotic therapy in an infection site for up to 30 days as antibiotic passively diffuses across a rate-controlling membrane. It received Breakthrough Device Designation by the FDA, is a drug-led combination products, and a pre-investigational new drug (IND) application is currently being reviewed by CDER. We recently completed a GLP safety study to support FDA review. Once an IND is approved, we will perform our first-in-human clinical trial. We think it would be highly valuable for the scientific community to learn about the Purgo Pouch mechanics and outcomes, our regulatory experience, FDA interactions, and what it takes to transition a drug-led combination product through the FDA process.

Methods

Using an established sheep model of biofilm-inoculated, fracture-related infection, Purgo Pouch efficacy has been tested in over 200 sheep to date and compared to clinical standards of care—e.g., antibiotic powder sprinkling, and antibiotic-loaded $CaSO_4$ beads—in another 100 sheep. Just two weeks ago, completed a GLP safety study of tobramycin and the Purgo Pouch in 4 sheep; the Purgo Pouch was surgically implanted over simulated fractures and simulated fracture fixation plates in the right tibia of each sheep and refilled each day with 352 mg tobramycin for 30 days. A sham surgery was performed in the left leg for comparison. Histological data were collected and a semi-quantitative histopathology report generated. Local tissue and clinical pathology (blood work) outcomes were assessed per the ISO 10993 family. All sheep work was performed with a 1:1 male to female ratio in study groups.

Results

Efficacy data showed that the Purgo Pouch kills upwards of 1,000x more bacteria and treats infection more effectively than any standard of care. Histological data corroborated microbiological outcomes. GLP safety data showed that fracture lines of Purgo Pouch-treated sites healed even better than sham surgical sites (Fig. 1), and local soft tissues had a slight reaction. Creatinine levels remained the same in all four GLP sheep, suggesting the tobramycin dose was safe systemically.

Discussion

In a group of sheep that received systemic antibiotic therapy, wound sites did not display significant infection while antibiotics were administered, but once therapy was discontinued, infection flared, which is consistent with the known and challenging pattern of biofilm-related infection. Positive histological outcomes answered one of the most poignant questions related to the Purgo Pouch technology: does up to 30 days of local antibiotic therapy adversely affect local host tissue? In efficacy studies, bacteria were killed to a sufficient level that host bone was able to heal, suggesting that treatment was effective but not toxic. The GLP safety study outcomes likewise indicated that up to 352 mg of tobramycin delivered via the Purgo Pouch each day did not adversely affect surgical site healing. Safety and efficacy outcomes strongly support the potential for the Purgo Pouch to be evaluated in a first-in-human clinical trial.

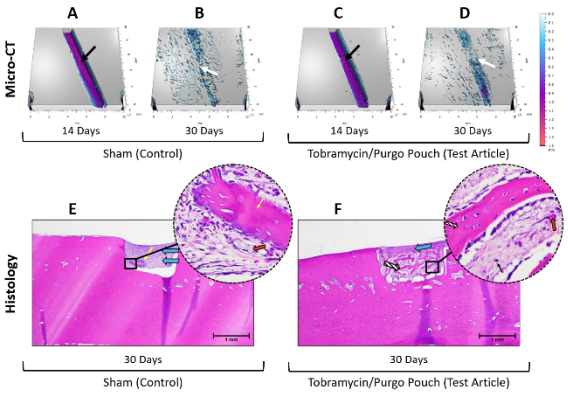

Figure 1: (**Top panel**) Micro-CT images of sheep samples from a non-GLP study. (A & C) Minimal cortical bone changes were observed at 14 days in the sham and Pouch sites with no bone growth in the fracture line (black arrows). (B & D) Increased surface porosity and new bone within the fracture line (white arrows) by 30 days. (**Bottom panel**; E & F) Histological sections collected in the GLP study showed that by 30 days, Pouch-treated sites had visible woven bone filling the void along with increased cortical porosity. Osteoblasts actively lined the new bone surfaces in sheep treated with tobramycin/Purgo Pouch, with notably more bone in the fracture line compared to sham sites, which still had resorbing bone chips. All bones were healing without toxic effects.

Significance/Clinical Relevance

The Purgo Pouch has significant potential to address major unmet needs in FRI management. If approved by the FDA under the 505(b)(2) pathway, it will be the first-ever drug delivery device to have specific indications for delivering tobramycin via passive diffusion and treating FRIs that are complicated by biofilm. Understanding how to navigate the FDA with a new product is crucial to truly improving clinical care.

Acknowledgment and Disclaimer

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