Pilot In Vivo Evaluation of a Resorbable, Antibiotic-Eluting Bone Void Filler to Prevent Periprosthetic Joint Infection

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Statement of Purpose: A resorbable composite antibiotic-eluting bone void filler was developed to address the high (17.5%)[1] infection rate associated with revision total joint replacement (TJR) procedures and even higher (20-30%)[2] rate of recurrent infections. This unique resorbable, composite, antibiotic-eluting bone void filler (AEBVF) provides two functional platforms: 1) an osteoconductive matrix for bone restoration and 2) local, extended antibiotic delivery to treat acute and chronic infections associated with revision TJR. Previous *in vitro* evaluations of this AEBVF demonstrated favorable extended antibiotic elution kinetics, providing antimicrobial activity up to 10 weeks against *Staphylococcus aureus* (*S. aureus)* strains with some formulations. Subsequent *in vivo* preclinical testing in two separate studies using a rabbit model demonstrated the bactericidal capacity of the AEBVF against a bacterial challenge of 10^7 CFU *S. aureus* in an acute model of periprosthetic infection, as well as the osteoconductivity of the AEBVF. We hypothesized that a polymer/ceramic composite could restore bone volume while eliminating a periprosthetic bacterial burden of 10^5 CFU using the novel AEBVF in a pilot study utilizing a sheep femoral condyle defect model.

Methods: The experimental protocol was approved by Institutional Animal Care and Use Committees (IACUC) at CoorsTek Medical (Logan, UT). AEBVF devices (2 mm x 2 mm x 6 mm) comprising poly(caprolactone) (PCL), poly(ethylene glycol) (PEG), poly(lactide-co-glycolide) (PLGA, 50:50), ProOsteon granules (Biomet, USA; sieved 150-425 µm), $CaCl_2$, and tobramycin. Four groups were utilized in this pilot large animal *in vivo* study (Figure 1). To assess performance, six sterilized devices were surgically implanted in a rectangular defect (7 mm x 9 mm x 7.5 mm) in the medial face of the femoral condyle of each sheep. "Control" groups utilized ProOsteon and "Challenge" groups utilize the novel AEBVF.

Table 1*: Groups utilized to assess osteoconductivity (Groups A&B) and bactericidal capacity (Groups C&D).*

Group	Implant type	Number	Duration
A	Osteoconductive Control - ProOsteon	2	12 weeks
B	Osteoconductive Challenge - AEBVF	2	12 weeks
C	Infection Control –w/ *S. aureus* (10^5)	2	12 weeks
D	Infection Challenge –w/ *S. aureus* (10^5)	2	12 weeks

At 12 weeks, the bone-implant interface was evaluated using micro-computed tomography (µ-CT), backscatter electron microscopy, as well as standard histology and histomorphometry procedures.

Results: All animals in the "Osteoconductive" groups survived to the study's 12-week endpoint. Qualitative and quantitative µ-CT analysis supported osteoconductive nature of both Groups A&B, with complete restoration of the surgically created defect observed after 12 weeks (Figure 1). Notably, the novel AEBVF showed more complete bone remodeling after 12 weeks. Evaluation of the bone volume ratio (BV/TV) indicated greater bone volume in the *Challenge* than the *Control* (51.9 ± 10% vs. 39.6 ± 4%). Also notable was that the implant volume (IV/TV) of the AEBVF *Challenge* was significantly diminished (0.16 ± 0.1%) after 12 weeks, as compared to the *Control* (13.23 ± 3.2%) and Time "0" (16.8%) values.

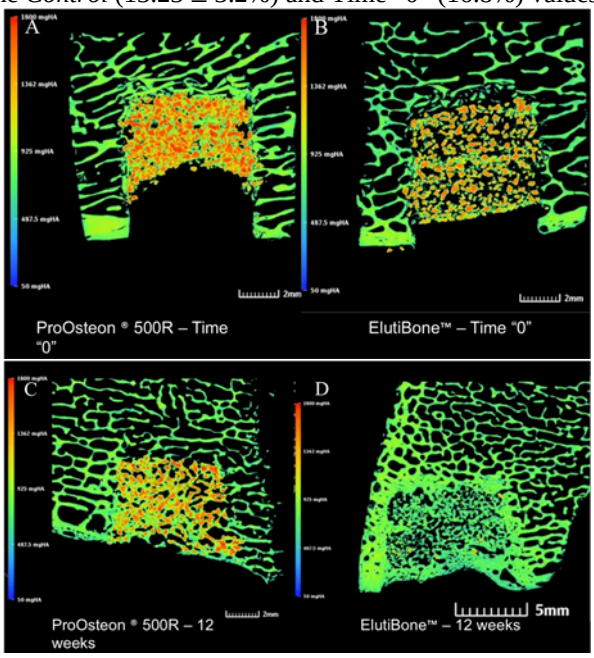

Figure 2: µ-CT images of Time "0" Osteoconductive Control (A) and Challenge (B) and 12-week control (C) and challenge (D).

Preliminary evaluation of the Infection groups (Groups C&D) showed both *Challenge* animals to survive the 12 week study with no signs of infection. In contrast, both *Control* animals were euthanized 11 days post-op.

Conclusions: The novel resorbable, antibiotic eluting bone void filler appears to possess both osteoconductive and bactericidal properties. In previous *in vitro* studies[3], the AEBVF has shown the ability to elute antibiotic for up to 7 weeks at bactericidal concentrations. Significant degradation was also observed *in vitro*. Consistent with these findings, these data show the ability to 1) eliminate a periprosthetic *S. aureus* burden of 10^5 colony forming units, 2) promote bone remodeling superior to a known bone void filler, and 3) degrade at a rate that does not interfere with host bone remodeling. Evaluation of the histology and histomorphometry data is ongoing.

References: 1. Kurtz S MF, Ong K, Chan N, Lau E, Halpern M., JBJS (Am) 2005;87(7):1487-1497.
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