INTRODUCTION:
An estimated 600,000 bone grafting procedures are done annually in the United States. Despite the increase in the number of procedures that require bone grafts, the optimal bone graft substitute has not been defined. Synthetic bone graft substitute are osteoconductive and consist of hydroxyapatite, tricalcium phosphate, calcium sulfate, or a combination of these minerals. All synthetic porous substitutes share numerous advantages over autografts and allografts including their unlimited supply, easy sterilization, lack of disease transmission, and long-term storage. Infection and nonunions are common complications of surgical repair that require bone grafts and hardware due to trauma, cancer treatment, spine surgery or revision surgery. Although the routine use of antibiotic prophylaxis in orthopaedic surgery has been shown to be beneficial, the effectiveness of intravenous antibiotic administration is often complicated by insufficient local drug delivery. Hence, the development of a bone substitute that can also serve as a local drug delivery system may be beneficial in patients with open fractures or patients who are at risk for developing a bone infection. The purpose of this study is to report our preclinical and clinical experience with the use of a novel antibiotic-impregnated calcium sulfate/carbonate based bone graft substitute.

METHODS:
The novel bone substitution material (Herafill® beads G) is a bioabsorbable bone substitute composed of calcium sulphate, calcium carbonate and glycerin tripalmitate as bonding additive containing 4mg gentamicin sulphate corresponding to 2.5mg gentamicin.

A. Preclinical investigation
Five adult New Zealand white rabbits (average weight of 3.5kg, closed epispidyphal plate) were employed for this study. A defect was drilled in the femoral condyle of the right rabbit knee and two Herafilf® beads G were inserted into the cavity. Animals were sacrificed at 6, 12 and 24 weeks and graft incorporation was assessed using histology, radiographs, and microCT.

B. Clinical investigation
In an open, not randomized clinical trial actually 11 patients were recruited and operated upon. Five adult New Zealand white rabbits (average weight of 3.5kg, closed epispidyphal plate) were employed for this study. A defect was drilled in the femoral condyle of the right rabbit knee and two Herafill® beads G were inserted into the cavity. Animals were sacrificed at 6, 12 and 24 weeks and graft incorporation was assessed using histology, radiographs, and microCT.

For the evaluation of the absorption and mineralization process of the calcium sulfate/carbonate based bone substitute, radiographs were obtained within the first week, 3 months, and 6 months postoperatively. In addition, disease state (progression or healing of osteomyelitis) was assessed by comparison to preoperative (baseline) and postoperative (day 2 and day 21) biopsies. The specimen was embedded in MMA, cut and prepared for thin section. Histological investigation demonstrated implant absorption and mineralization. The absorption process was mostly associated with the presence of mononuclear phagocytes. Giant cells were absent. Osteogenesis was highly distinct. Active osteogenesis with newly formed osteoid was abundant in spite of high cellular infiltrates of lysosomal phagocytes.

RESULTS:
A. Preclinical investigations
Histological investigation demonstrated implant absorption and mineralization. The absorption process was mostly associated with the presence of mononuclear phagocytes. Giant cells were absent. Osteogenesis was highly distinct. Active osteogenesis with newly formed osteoid was abundant in spite of high cellular infiltrates of lysosomal phagocytes.

B. Clinical investigations
Histological analyses of a bone biopsy clearly demonstrated an intensive cellular reaction (predominantly phagocytes) during the implant degradation followed by osteoid formation.

Clinically, the results from the preclinical data were confirmed. Radiographic analyses showed a biologically adapted resorption of the graft material followed by new bone formations. In addition, high levels of gentamicin could be detected (up to 1600ng).

DISCUSSION:
In summary, radiographic and histological analyses demonstrated that Herafill® beads G are a biocompatible, absorbable calcium sulphate/carbonate based bone void filler. New bone formation and implant mineralization was increased with increased duration of implantation. No inflammatory reaction or adverse events were observed clinically. In addition, high gentamicin levels in the area of application confirmed that this new bone substitute did not only serve as an excellent biomaterial but also provided excellent anti-infective properties at the surgical site.