White Paper 4 – Degradation of BoneWelding® Implants does not trigger excessive inflammatory reaction

Inflammatory processes and polymer resorption

The acute inflammatory response after implantation of resorbable implants is comparable to that of non-resorbable materials. During the remodeling phase, the inflammatory response is very mild. Then, after 12 months, the late degradation phase induces a mild inflammatory response due to the large polymer mass and the resorption process while removing the material. Macrophages and giant foreign body cells are generally present during late degradation and remodeling for new bone formation, especially in combination with a degradable material [1-3]. As long as there is no excessive fibrous capsule formation, their presence does not mean that the bioresorbable implant is not biocompatible [1, 4]. Late local inflammatory reactions are a common effect during the degradation of polymers; they usually do not trigger an immune system response nor an allergic reaction [5]. A harmful inflammatory response can be prevented if the degradation rate is slow enough for the body to keep up with metabolizing the polymer debris [6].Furthermore, PLDLLA keeps its amorphous character -even under degradation conditions- and does not lead to crystallites which may trigger a late chronic response as observed for semicrystalline poly-L-lactide (PLLA) [7, 8].

Inflammatory response for PLDLLA implants inserted with BoneWelding® Technology

The safety aspects of ultrasonically inserted PLDLLA and the material properties themselves were evaluated in several *in vivo* studies.
In a 12 months ovine study [9], polymeric pin-like implants were inserted into bone either by applying the BoneWelding® Technology or manually by press-fit. The comparative studies provided evidence that local, controlled melting of a polymer does not negatively affect acute tissue reaction, osseointegration, and resorption of the polymer implants. Over the whole observation period (2 weeks, 6 months, and 12 months – *Figure 1, Figure 2, Figure 3*), no difference in bone formation and remodeling was observed between implants attached with the BoneWelding® Technology to those inserted manually by press-fit. After 12 months, the faster-degrading PDLLA (used for the VetWelding Resorb Pin and Plate System) was resorbed completely, and the pin was replaced by bone. The slower degrading PLDLLA (used in the Weldix® Anchor) showed early dissolution but without enhanced inflammatory reaction. As proven in a later 24 months sheep study, this polymer takes about 18 to 24 months to resorb entirely and be substituted by bone.

BoneWelding® Pin of PLDLLA
(Weldix® Anchor)

Press-fitted Pin of PLDLLA (Control)

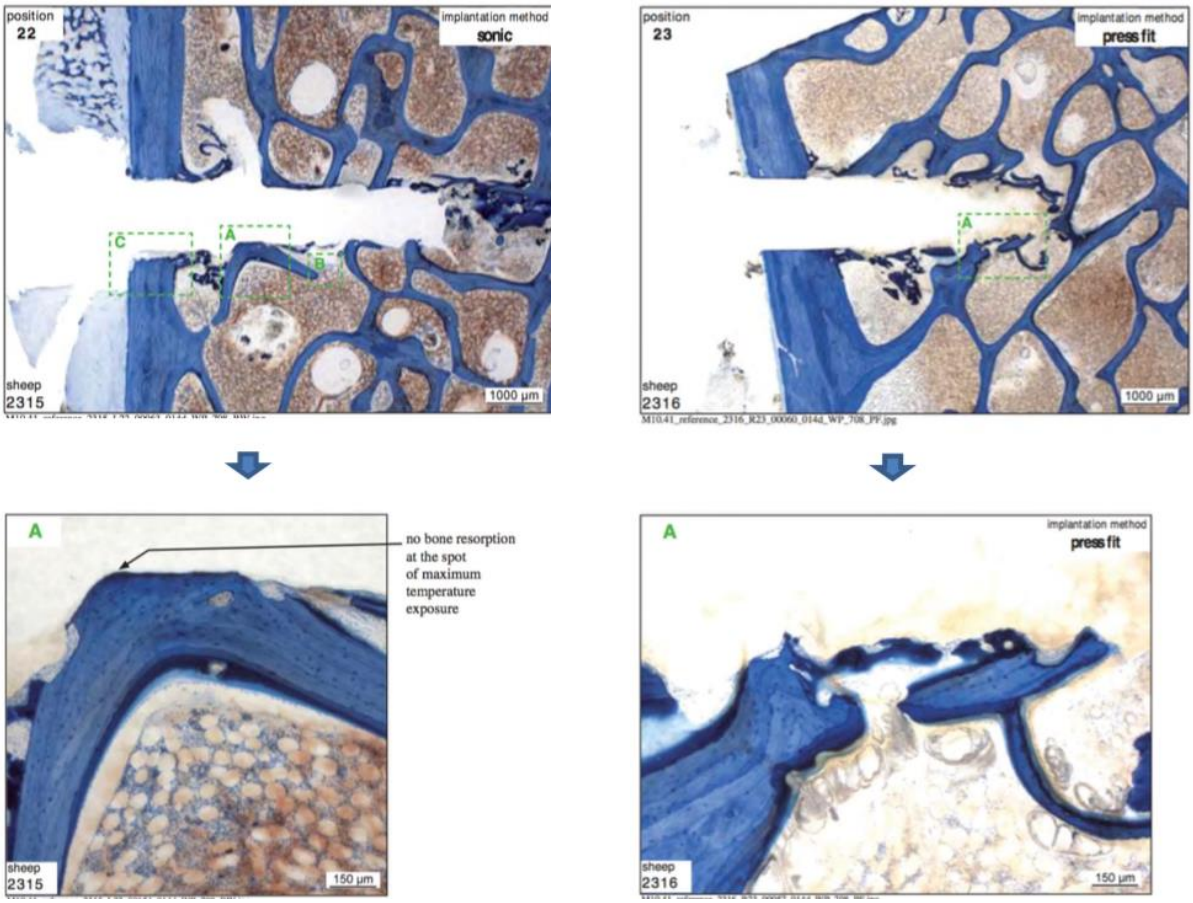


Figure 1: PLDLLA Pin implants – comparison of a BoneWelding® and a manually inserted press-fit pin – 2 weeks post-op, toluidine blue staining. No difference in acute bone reactions between the two insertion methods.

BoneWelding® Pin of PLDLLA
(Weldix® Anchor)

Press-fitted Pin of PLDLLA (Control)

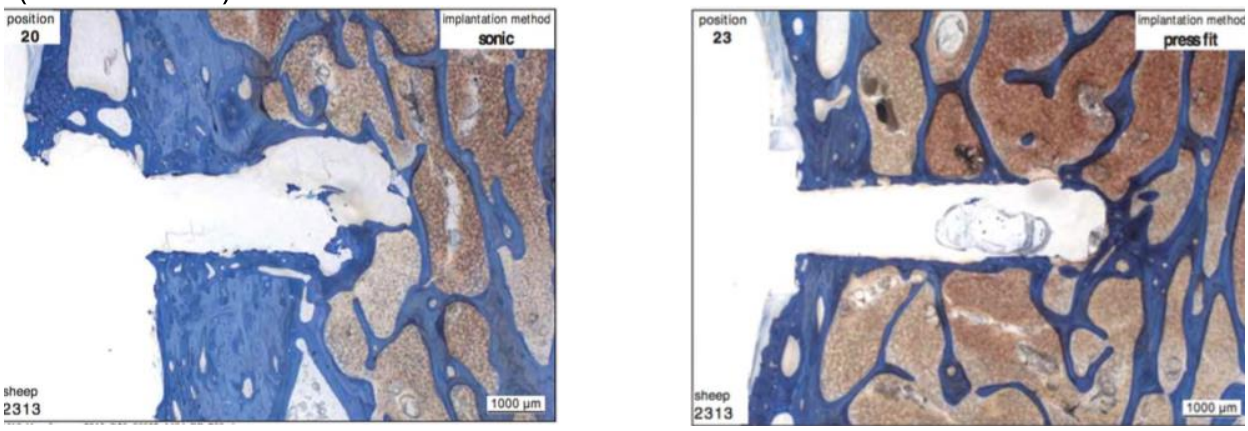
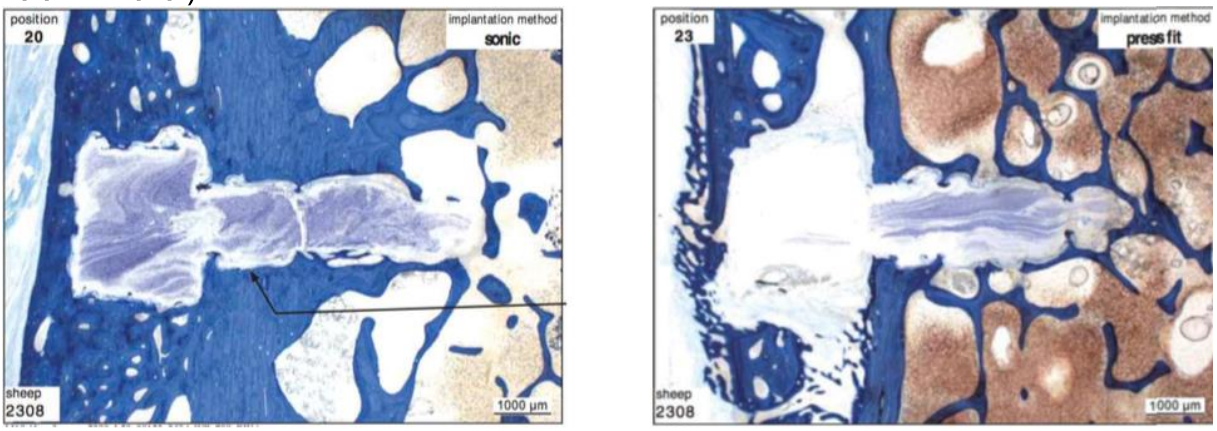


Figure 2 PLDLLA Pin implants – comparison of a BoneWelding® and a manually inserted press-fit pin – 6 months post-op [9]. No difference in bone remodeling reactions between the two insertion methods; no fibrous membrane formation; both implants show first signs of resorption of the implant surface.

BoneWelding® Pin of PLDLLA
(Weldix® Anchor)

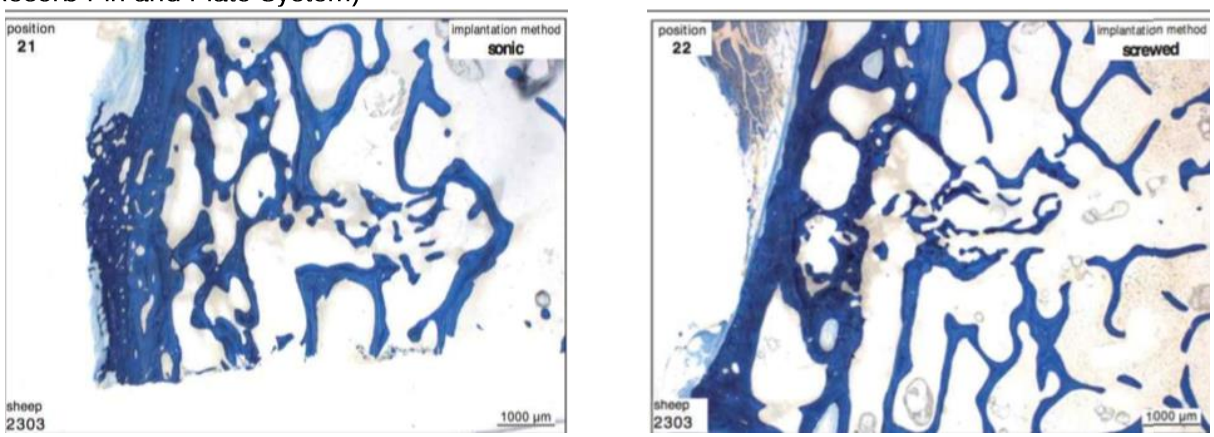
Press-fitted Pin of PLDLLA (Control)



No difference in bone reactions between the two insertion methods: no fibrous membrane formation; both implants show advanced polymer resorption and disintegration; no signs of bone lysis

Bone Welding® Pin of PDLLA
(Resorb Pin and Plate System)

Press-fitted Pin of PDLLA (Control)



Comparison of implants made of the faster resorbing Resomer® R208 inserted either by the BoneWelding® Technology or by press fit. Irrespective of the implantation method, implants show complete resorption and replacement by new bone, no signs of bone lysis or of fibrous membrane formation.

Figure 3: Pure polymer implants – comparison of a BoneWelding® and a manually inserted press-fit pin, both for the slower (LR708) and the faster (R208) resorbing PLA – 12 months post-op [4].

Discussion

Ultrasonically inserted implants provide a unique interface that immediately provides primary stability through the anchorage in bone [10]. An excellent primary stability reduces the risk for micromotion, implant loosening, and a thereby induced excessive inflammatory reaction.

Numerous additional animal studies on the BoneWelding® Technology have confirmed the above findings. In one of the first studies, PLDLLA pins and coated titanium implants were inserted into the ovine femur and tibia and evaluated 2 and 6 months after implantation. They found new bone formation without evidence of an inflammatory reaction for the pin implants and the titanium coated implants [11].

Another study investigated PLDLLA pin and plate implants inserted employing BoneWelding® in the ovine cervical vertebra. They found no inflammatory cell reaction in the adjacent bone nor adverse effects in the heat-sensitive nerves and vessels in response to the ultrasonic insertion technology two months after surgery [12]. Good biocompatibility and physiological remodeling of the tendon-bone interface were observed in a study involving anterior cruciate ligament repair with a titanium dowel fixed by polymer extrusion employing

inside-out BoneWelding® Technology in 18 sheep [13]. A study in 11 sheep in cranial applications of BoneWelding® implants observed no inflammatory and soft tissue reactions with polymer pins [14].
Another study in 18 sheep reported on no seromas and no infection, even after 36 months. Henceforth, the authors concluded that biodegradable polymers such as PLDLLA do not lead to clinically significant inflammation [15]. No critical signs of inflammatory response were observed in the first 20 weeks in 4 sheep in this further study [16]. A study in a caprine model reports good biocompatibility [17], whereas the use of bioabsorbable materials is supported *in vivo* by the authors of another study [18]. Similar findings have been observed in earlier studies, e.g., by *Saiku-Backstrom et al.* They used PLDLLA plates in 12 toy breed dogs, no abnormal bone reactions or foreign body reactions were observed. The degradation was well tolerated, although the plates were placed subcutaneously [19].
Clinical studies on BoneWelding® implants in humans report no foreign body reaction, no osteolysis around the implant, and hence no chronic inflammatory response [20, 21]. However, in human patients, mild responses during the late degradation phase have been observed for subcutaneously placed PDLLA plates in craniomaxillofacial applications. In some patients, the reactions have been associated with local swelling that disappeared again after a few weeks [22]. Such swelling responses have not been described for implants placed into bone such as pins or suture anchors.
Care has to be taken, though, in applying the polymer without proper metal support to highly loaded and mechanically unstable cases, as studies investigating the use of the polymer for unsupported spinal cages indicate. Here the excessive load on the implants leads to creep behavior, mechanical instability, and disintegration of the cages, which causes an intense inflammatory reaction and accelerated degradation [23-25]. However, those observed device failures and inflammatory reactions are a consequence of the choice of the wrong indication with excessive mechanical load (see also White Paper 3). The BoneWelding® implants are designed for specific, clinically and mechanically tested and approved indications that demonstrate a suitable use of a biodegradable implant.

In conclusion, the results from different animal models and clinical studies all indicate a **safe use of biodegradable polymers in small animals; the inflammation is described as non-existent to mild**. Slight swelling can occur in subcutaneously placed plates, which is not expected for the implants placed directly in bone by BoneWelding® Technology. **In the correct indication, the polymer resorbs completely and transforms into bone with any sign of unwanted histological reaction or even osteolysis.**

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